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(54) 2-ACYLOXYCEPHEM DERIVATIVES AS ELASTASE INHIBITORS

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Description

[0001] The present invention relates to new cephalosporins, their preparation and to pharmaceutical and veterinary compositions containing them.

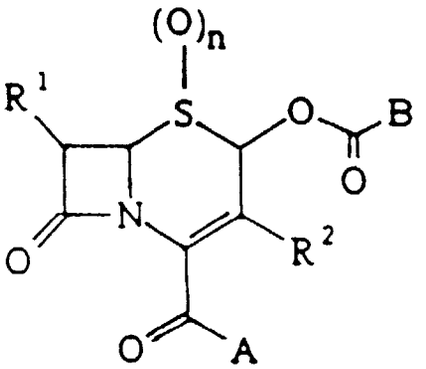
[0002] The compounds disclosed in the present invention are cephem sulphones or sulphoxides featuring the simultaneous presence on the cephem skeleton of an acyl group at C-4 and an acyloxy group at C-2.

[0003] FR-A-2020063 describes 2-acyloxy-4-carboxy-7-aminoprotected cephems having antibiotic activity.

[0004] WO91/09036 provides cephems with an acyl group at C-4 and a-$S(O)_n$-linking group at C2 which are endowed with inhibitory activity on elastases.

[0005] EP-A-0337704 discloses 4-acyl cephems without substituent at the C-2 position with elastase inhibitory activity.

[0006] According to the invention there are provided cephalosporin sulphones of formula (I) and the pharmaceutically and veterinarily acceptable salts thereof:



(I)

wherein n is one or two:

A and B are each, independently, hydrogen or an organic radical selected from optionally substituted C_1-C_{12} straight or branched alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, or C_7-C_{18} aralkyl, C_8-C_{18} aralkenyl, C_8-C_{18} aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl and (heterocyclyl)alkenyl groups; the substituents, when present, being selected from the list herein below;
R^1 represents

(1) a chlorine, fluorine, bromine or iodine atom
(2) A as defined above
(3) an ether OA wherein A is as defined above
(4) a thioether, sulphoxide or sulphone -$S(O)_m$A wherein m is either zero, one or two and A is as defined above;
(5) acyloxy -OC(O)A wherein A is as defined above;
(6) sulphonyloxy -$OS(O)_2$A wherein A is as defined above;
(7) an acylamino group -NHC(O)A wherein A is as defined above or acylamino -NH-Z wherein Z is a mono, di- or tripeptide composed of D or L α-aminoacids chosen from Ala, Gly, Val, Leu, Ile and Phe, and in which α-amino acids the terminal amino group is either free or acylated by a group -C(O)A or -C(O)OA wherein A is as defined above;

R^2 represents:

(1) A as defined above;
(2) a chlorine or fluorine atom;
(3) a sulphenyl, sulphinyl or sulfonyl group -$S(O)_m$A wherein A is as defined above;
(4) an oxy group -O-A wherein A is as defined above;
(5) an acyl group -C(O)A or acyloxy group -C(O)OA wherein A is as defined above;
(6) an oxymethyl group -CH_2-OA wherein A is as defined above;
(7) a thiomethyl group or a derivative thereof of formula -$CH_2S(O)_m$A wherein m and A are as defined above;
(8) an acyloxymethyl group -$CH_2OC(O)$A or -CH_2O-Z wherein A and Z are as defined above;

(9) an acylthiomethyl group -$CH_2SC(O)A'$ wherein A is as defined above;
(10) an aminomethyl group -CH_2-N(A)A' wherein A is as defined above and A', being the same or different, is as defined above for A; or A and A' taken together with the nitrogen atom to which they are attached represent a heterocyclic ring;
(11) ammoniomethyl -$CH_2N^+(A)(A')A''$ wherein A and A' are as defined above and A", being the same or different, is as defined for A; or A is alkyl and A' and A" together with the nitrogen atom to which they are attached represent a heterocyclic ring, or A and A' and A" together with the nitrogen atom to which they are attached represent a heterocyclic ring;
(12) an acylaminomethyl group -CH_2NH-C(O)A or -CH_2NH-Z wherein A and Z are as defined above.

[0007] As referred to herein a C_1-C_{12} alkyl group is straight or branched, for instance C_1-C_{10} alkyl, typically C_1-C_6 alkyl or C_1-C_4 alkyl. Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and so on.

[0008] A C_2-C_{12} alkenyl group is straight or branched, for instance C_2-C_{10} alkenyl, typically C_2-C_6 alkenyl or C_2-C_4 alkenyl. Examples include vinyl, allyl, crotyl, 2-methyl-1-propenyl, 1-methyl-1-propenyl, butenyl, pentenyl and so on.

[0009] A C_2-C_{12} alkynyl group is straight or branched, for instance C_2-C_{10} alkynyl, typically C_2-C_6 alkynyl or C_2-C_4 alkynyl. Examples include ethynyl, propargyl, 1-propynyl, 1-butynyl, 2-butynyl and so on.

[0010] A C_6-C_{14} aryl group is preferably a monocyclic, bicyclic or tricyclic aromatic hydrocarbon group of 6 to 14 carbon atoms, such as phenyl, naphthyl, phenanthryl or anthryl.

[0011] A C_3-C_8 cycloalkyl group is preferably a saturated carbocyclic group of 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and so on.

[0012] A C_5-C_8 cycloalkenyl group is preferably an unsaturated carbocyclic group such as cyclopentenyl, cyclohexenyl and so on.

[0013] A C_7-C_{18} aralkyl group is preferably an alkyl group of 1 to 4 carbon atoms linked to a monocyclic, bicyclic or tricyclic aromatic hydrocarbon group of 6 to 14 carbon atoms. Examples of aralkyl groups are benzyl, phenylethyl, naphthylmethyl, naphtylethyl and anthrylmethyl.

[0014] A C_8-C_{18} aralkenyl group is preferably an alkenyl group of 2 to 4 carbon atoms linked to a monocyclic, bicyclic or tricyclic aromatic hydrocarbon group of 6 to 14 carbon atoms. Examples of aralkenyl groups are styryl, 2-phenyl-1-propenyl, 3-phenyl-2-butenyl, 2-naphthylethenyl, anthrylethenyl and so on.

[0015] A C_8-C_{14} aralkynyl group is preferably an alkynyl group of 2 to 4 carbon atoms linked to a monocyclic, bicyclic or tricyclic aromatic hydrocarbon group of 6 to 10 carbon atoms. Examples of aralkynyl groups are 2-phenylethynyl, 2-naphthylethynyl, anthrylethynyl and so on.

[0016] A (cycloalkyl)alkyl group is preferably an alkyl group of 1 to 4 carbon atoms linked to a cycloalkyl group.

[0017] A (cycloalkyl)alkenyl group is preferably an alkenyl group of 2 to 4 carbon atoms linked to a cycloalkyl group or to an aryl group.

[0018] A heterocyclyl group is preferably a 3- to 6-membered, saturated or unsaturated heterocyclyl ring, containing at least one heteroatom selected from O, S and N, which is optionally fused to a second 5- or 6-membered, saturated or unsaturated heterocyclyl group or to a cycloalkyl group or to an aryl group.

[0019] A (heterocyclyl)alkyl group is preferably an alkyl group of 1 to 4 carbon atoms linked to a heterocyclyl group.

[0020] A (heterocyclyl)alkenyl group is preferably an alkenyl group of 2 to 4 carbon atoms linked to a heterocyclic group.

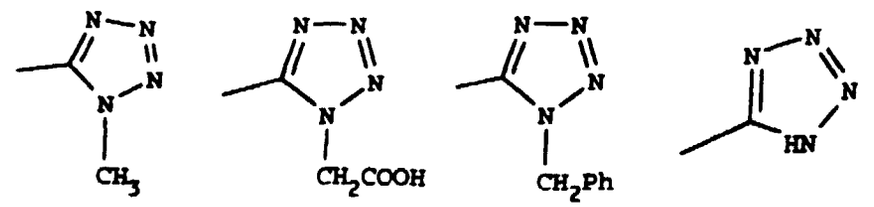
[0021] The term halogen or halo preferably denotes fluorine, chlorine or bromine.

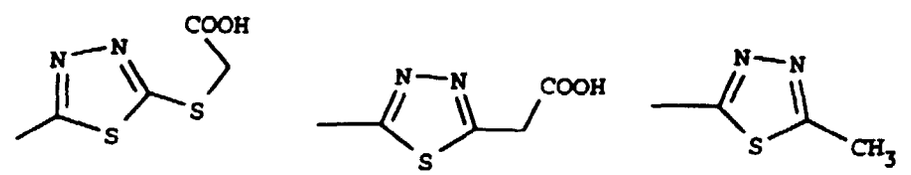
[0022] The above said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, aralkenyl, aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl and (heterocyclyl)alkenyl groups can be either unsubstituted or substituted by one or more substituents selected from:

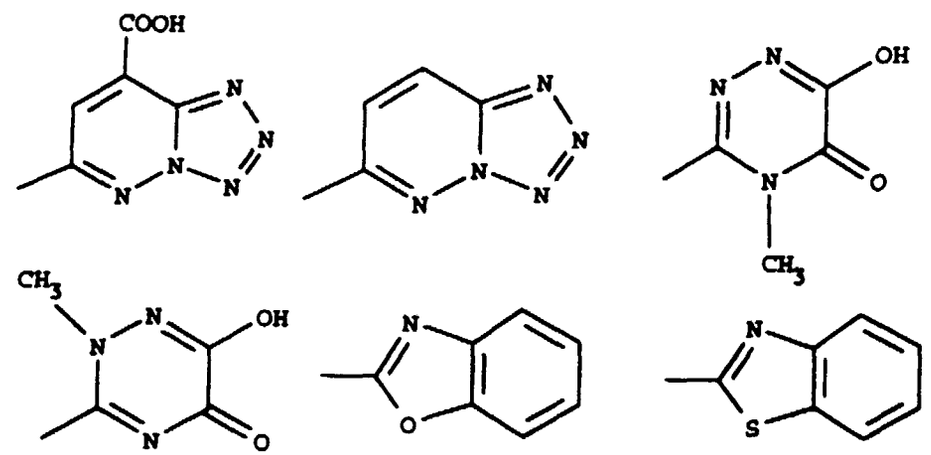
- halo (e.g., fluoro, bromo, chloro or iodo);
- hydroxy;
- nitro;
- azido;
- mercapto (-SH);
- amino (i.e., $-NH_2$, or $-NHR^i$ or $-NR^iR^{ii}$) wherein R^i and R^{ii}, which are the same or different, are C_1-C_{12} straight or branched alkyl or phenyl or benzyl; or phenyl optionally substituted by one or more halogen atoms or carboxy groups;
- formyl (i.e., -CHO);
- cyano;
- carboxy(alkyl) (i.e., $(CH_2)_tCOOH$ or $(CH_2)_tCOOR^i$) wherein R^i is as defined above and t is 0, 1, 2 or 3;
- sulfo (i.e., $-SO_3H$);

- acyl (i.e., -C(O)R^i) wherein R^i is as defined above or trifluoroacetyl (i.e., -C(O)CF_3);
- carbamoyl (i.e., -$CONH_2$); N-methylcarbamoyl (i.e., -$CONHCH_3$) or N-carboxymethylcarbamoyl (i.e., -$CONHCH_2COOH$);
- carbamoyloxy (i.e., -$OCONH_2$);
- acyloxy (i.e., -OC(O)R^i) wherein R^i is as defined above or formyloxy (i.e., -OC(O)H);
- alkoxycarbonyl or benzyloxycarbonyl (i.e., -C(O)OR^i) wherein R^i is as defined above;
- alkoxycarbonyloxy or benzyloxycarbonyloxy (i.e., -OC(O)OR^i) wherein R^i is as defined above;
- alkoxy, phenoxy or benzyloxy (i.e., -OR^i) wherein R^i is as defined above;
- alkylthio, phenylthio or benzylthio (i.e., -SR') wherein R^i is as defined above;
- alkylsulfinyl, phenylsulfinyl or benzylsulfinyl (i.e., -S(O)R^i) wherein R^i is as defined above;
- alkylsulfonyl, phenylsulfonyl or benzylsulfonyl (i.e., -$S(O)_2R^i$) wherein R^i is as defined above;
- acylamino (i.e., -NHC(O)R^{iii} or -NHC(O)OR^{iii}) wherein R^{iii} is C_1-C_{12} straight or branched alkyl, phenyl, benzyl, CH_2CH_2COOH or $CH_2CH_2CH_2COOH$;
- sulfonamido (i.e., -$NHSO_2R^i$) wherein R^i is as defined above;
- guanidino (i.e., -NHC(=NH)NH_2);
- C_1-C_4 alkyl, C_2-C_4 alkenyl or alkynyl;
- C_3-C_6 cycloalkyl;
- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl, cyanomethyl, carboxymethyl, sulfomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl, C_1-C_4 alkyloxycarbonylmethyl, guanidinomethyl.
- phtalimido, indolyl, indolinyl, isoindolinyl, 1-oxoisoindolinyl.

[0023] The heterocyclic group may in particular be chosen from:

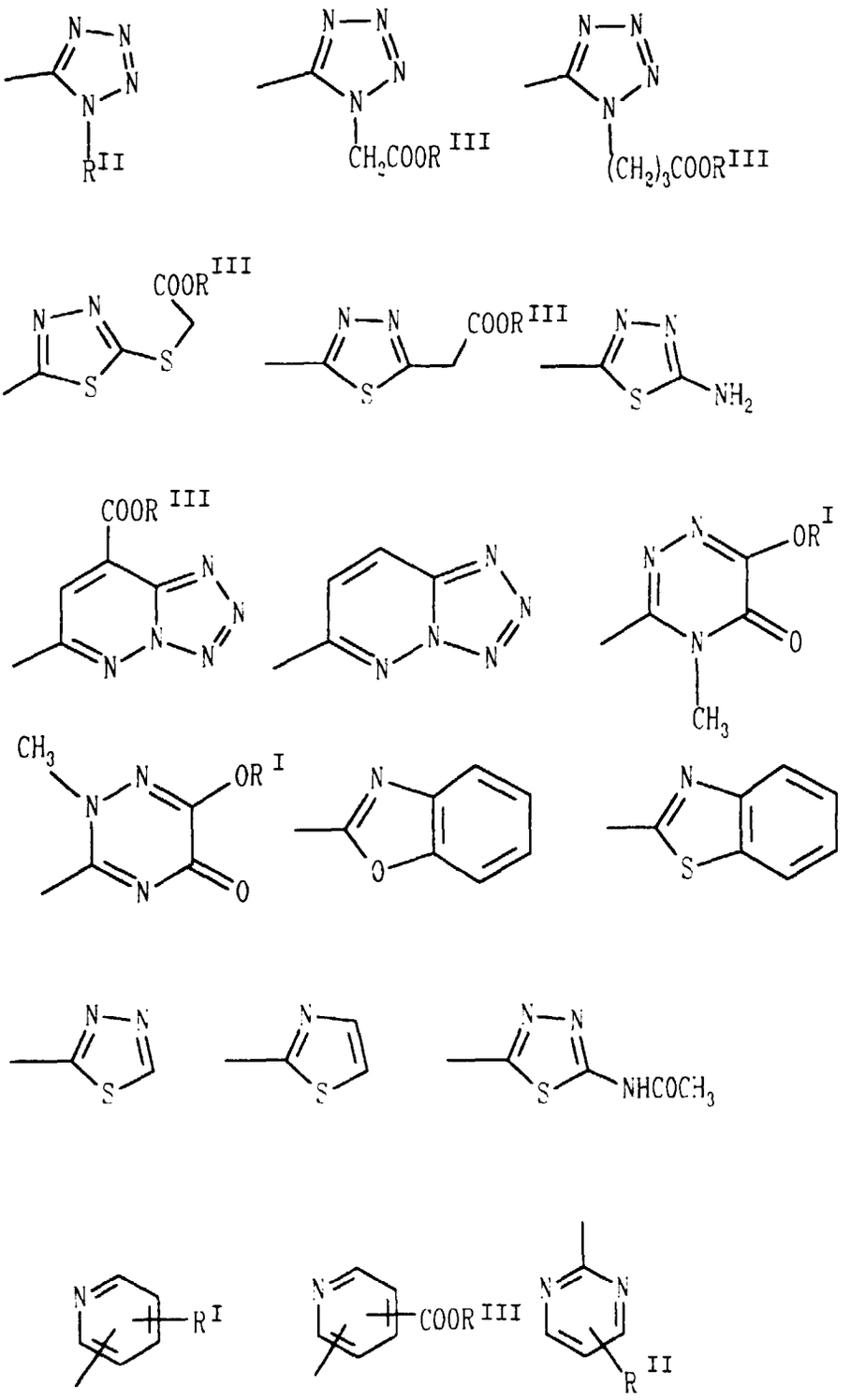






[0024] Any of the above heterocyclic groups may be totally or partially reduced.

[0025] More preferably, the heterocyclic group is chosen from:



wherein R^I is, typically, hydrogen, methyl, allyl or benzyl, or a hydroxy protecting group; R^{II} is hydrogen, methyl, ethyl, propyl, phenyl, benzyl, carboxymethyl, 2-carboxyethyl, 3- carboxypropyl, 3-benzhydryloxycarbonylpropyl, sulphoethyl, 2,2-dimethylaminoethyl and R^{III} is typically hydrogen, methyl, allyl or benzyl or a carboxy protecting group.

[0026] The carboxy-protecting group may, for example, be a lower alkyl group such as methyl, ethyl, propyl, isopropyl

or tert-butyl; a halogenated lower alkyl group such as 2,2,2-trichoroethyl or 2,2,2-trifluoroethyl; a lower alkanoyloxyalkyl group such as acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, 1-acetoxyethyl, 1-propionyloxyethyl; a lower alkoxycarbonyloxyalkyl group such as 1-(methoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy) ethyl, 1-(isopropoxycarbonyloxy)ethyl; a lower alkenyl group such as 2-propenyl, 2-chloro-2-propenyl, 3-methoxycarbonyl-2-propenyl, 2-methyl-2-propenyl, 2-butenyl, cinnamyl; an aralkyl group such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl, bis(p-methoxyphenyl)methyl; a (5-substituted 2-oxo-1,3-dioxol-4-yl)methyl group such as (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl; a lower alkylsilyl group such as trimethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, triphenylsilyl; or an indanyl group; a phtalidyl group; a pyranyl group; a methoxymethyl or methylthiomethyl group; a 2-methoxyethoxymethyl group. Particularly preferred are a tert-butyl group, a p-nitrobenzyl group, a p-methoxybenzyl group, a benzhydryl group, a tert-butyldimethylsilyl, tert-butyldiphenylsilyl group or a propenyl group.

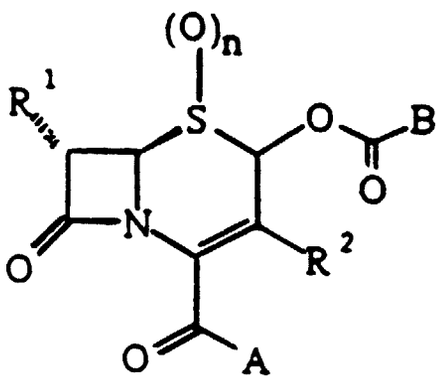
[0027] The amino, hydroxy or mercapto protecting groups which may optionally be present are any of those usually employed in the chemistry of penicillins and cephalosporins for this kind of function. They may be, for instance, optionally substituted, especially halo-substituted, acyl groups, e.g. acetyl, monochloroacetyl, dichloroacetyl, trifluoroacetyl, benzoyl or p-bromophenacyl; triarylmethyl groups, e.g. triphenylmethyl; silyl groups, in particular trimethylsilyl, dimethyl-tert-butylsilyl, diphenyl-tert-butylsilyl,; or also groups such as tert-butoxycarbonyl, p-nitrobenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyl and pyranyl. Preferred protecting groups of the hydroxy function are p-nitrobenzyloxycarbonyl; allyloxycarbonyl; dimethyl-tert-butylsilyl; diphenyl-tert-butylsilyl; trimethylsilyl; 2,2,2-trichloroethoxycarbonyl; benzyl; dimethoxybenzyl; p-methoxybenzyloxycarbonyl; p-bromophenacyl; triphenylmethyl, pyranyl, methoxymethyl, benzhydryl, 2-methoxyethoxymethyl, formyl, acetyl, trichloroacetyl.

[0028] The present invention provides the salts of those compounds of formula (I) that have salt-forming groups, especially the salts of the compounds having a carboxylic group, a basic group (e.g. an amino or guanidino group), or a quaternary ammonium group. The salts are pharmaceutically or veterinarily acceptable salts, for example alkali metal and alkaline earth metal salts (e.g. sodium, potassium, lithium, calcium and magnesium salts), ammonium salts and salts with an appropriate organic amine or amino acid (e.g. arginine, procaine salts), and the addition salts formed with suitable organic or inorganic acids, for example hydrochloric acid, sulphuric acid, carboxylic and sulphonic organic acids (e.g. acetic, trifluoroacetic, p-toluensulphonic acid). Some compounds of formula (I) which contain a carboxylate and an ammonium group may exist as zwitterions; such salts are also part of the present invention.

[0029] Furthermore, physiologically hydrolyzable esters, hydrates and solvates of compounds of formula (I) are included within the scope of the present invention. The physiologically hydrolyzable esters of the compounds (I) may include, for example, methoxycarbonylmethyl, 1-methoxycarbonyloxy-1-ethyl, indanyl, phthalidyl, methoxymethyl, pivaloyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl or 5-methyl-2-oxo-1,3-dioxolan-4-yl esters, and other physiologically hydrolyzable esters which have been widely used in the technical fields of penicillin and cephalosporin antibiotics: more preferably, methoxycarbonyloxymethyl, 1-methoxycarbonyloxy-1-ethyl, methoxymethyl or pivaloyloxymethyl; and most preferably, methoxycarbonyloxymethyl or methoxymethyl. Typical solvates of the cephalosporin compounds of formula(I) may include solvates with water miscible solvents, e.g. methanol, ethanol, acetone; or acetonitrile; and more preferably, ethanol.

[0030] The present invention also provides a pharmaceutical composition comprising, as an active principle, a compound of formula (I) or salt thereof, in association with one or more pharmaceutically acceptable carriers, excipients or other additives, if necessary.

[0031] The present invention encompasses all the possible stereoisomers of compounds of formula (I) as well as their racemic or optically active mixtures. However the configuration depicted in formula (1') is particularly preferred



(I')

wherein n is one or two;

A is hydrogen or C_1-C_{12} straight or branched alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, heterocyclyl, 2-phenyl-2-propyl, benzyl or diphenylmethyl, wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl and benzyl groups are either unsubstituted or substituted by fluoro, chloro, sulfo, carboxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, carbamoyl, sulfamoyl, carbamoyloxy, methanesulphonyl, nitro, cyano, diazo, hydroxy, methoxy, ethoxy, tert-butoxy, benzyloxy, benzhydryloxy, acetoxy, pivaloyloxy, benzoxy, carboxymethyl, carboxyphenyl C_6H_5-COOH, carboxybenzyl CH_2-C_6H_5-COOH, benzoyl, pivaloyl, amino, formamido, acetamido, trifluoroacetamido or pivalamido;

B is

(1') a hydrogen atom;
(2') an optionally substituted C_1-C_5 straight or branched alkyl or alkenyl group or C_3-C_6 cycloalkyl;
(3') optionally substituted C_6-C_{14} aryl;
(4') optionally substituted C_7-C_{15} aralkyl;
(5') optionally substituted heterocyclyl;
(6') optionally substituted (heterocyclyl)alkyl; the substituents for the groups defined under (1')-(6') being selected from fluoro, chloro, bromo, nitro, cyano, sulfo, carboxy, tetrazolyl, C_1-C_4 alkoxycarbonyl, carbamoyl,N-carboxyphenylcarbamoyl, N-carboxybenzylcarbamoyl, N-carboxymethylphenylcarbamoyl, sulfamoyl, carbamoyloxy, methanesulfonyl, hydroxy, C_1-C_4 alkoxy, benzyloxy, benzhydryloxy, phenoxy, p-chlorophenoxy, p-carboxyphenoxy, acetoxy, pivaloyloxy, benzoyloxy, methylthio, phenylthio, methanesulfonyl, benzenesulfonyl, carboxymethylthio, carboxyphenyl C_6H_5-COOH, carboxybenzyl CH_2-C_6H_5-COOH, acetyl, trifluoroacetyl, benzoyl, pivaloyl, amino, dimethylamino, phenylamino, 2,6-dichlorophenylamino diethylamino, formamido, acetamido, trifluoroacetamido, pivalamido, oxo, phenyl, phthalimido, isoindolinyl, 1-oxoisoindolinyl and C_1-C_5 straight or branched alkyl, vinyl or allyl, and C_1-C_4 alkyl substituted by one or more substituents selected from chloro, fluoro, difluoro, trifluoro, amino, N,N dimethylamino, azido, cyano, carboxy, sulfo, carbamoyl, carbamoyloxy, hydroxy, C_1-C_4 alkyloxycarbonyl, guanidino and a group Y-A''', wherein Y is oxygen, sulphur or carbamoyl(oxy) and A''' is an optionally substituted C_1-C_4 alkyl, phenyl, benzyl or heterocyclic group, the optional substituents being selected from those defined above for groups (1')-(5');

R^1 is

(1') hydrogen or a chlorine, fluorine or bromine atom
(2') C_1-C_4 alkyl, C_1-C_4 alkenyl, 1-(hydroxy)ethyl, 1-(benzyloxy)ethyl, 1-(benzyloxycarbonyloxy)ethyl, 1-(phenylacetoxy)ethyl, 2-fluoro-1-hydroxyethyl, phenyl or benzyl
(3') methoxy, ethoxy, isopropoxy, phenoxy or benzyloxy
(4') methylthio, ethylthio, isopropylthio
(5') formyloxy, acetoxy or phenylacetoxy
(6') mesyloxy or tosyloxy
(7') formamido, acetamido, fluoroacetamido, trifluoroacetamido or chloroacetamido
(8') R^{iv}-Ala-NH, wherein R^{iv} is acetyl, tert-butoxycarbonyl, benzoxycarbonyl or HOOC-$CH_2CH_2C(O)$-;
(9') R^{iv}-Val-NH, wherein R^{iv} is as defined above;
(10') Val-Pro-NH, LysNH or Ala-Ala-ProNH, wherein the terminal amino group of Val, Lys or Ala respectively or the α-amino group of Lys is either free or acylated with a group R^{iv} as defined above;

R^2 is either hydrogen or

(1') methyl, chloromethyl, bromomethyl, benzyl, ethyl, propyl or phenyl
(2') chloro
(3') methoxy or benzyloxy
(4') methylthio
(5') formyl, acetyl, benzoyl, carboxy, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl or benzyloxycarbonyl;
(6') methoxymethyl, ethoxymethyl, isopropoxymethyl; or benzyloxymethyl, phenoxymethyl, 3-pyridyloxymethyl wherein the phenyl and pyridyl rings are either unsubstituted or substituted by one group or two groups which are the same or different and are each chosen from hydroxy, carboxy, amino and C_1-C_4 alkoxycarbonyl;
(7') -$CH_2(S)_nA$ wherein n is zero, one or two and A is as defined above;
(8') acetoxymethyl, benzoyloxymethyl, phenylacetoxymethyl or C_3-C_6 alkanoyloxymethyl, which groups are

either unsubstituted or substituted by one or more groups selected from carboxy, hydroxy and C_1-C_3 alkoxy;
(9') trialkylammoniomethyl wherein the alkyl group is methyl, ethyl or propyl; N-methylpyrrolidiniomethyl, N-methylpiperidimiomethyl or N-methylmorpholiniomethyl;
(10') pyridiniomethyl which is either unsubstituted or substituted on the heterocyclic ring by fluoro, chloro, methoxy, hydroxy, carboxy or carbamoyl;
(11') carbamoyloxymethyl; or
(12') carboxy;

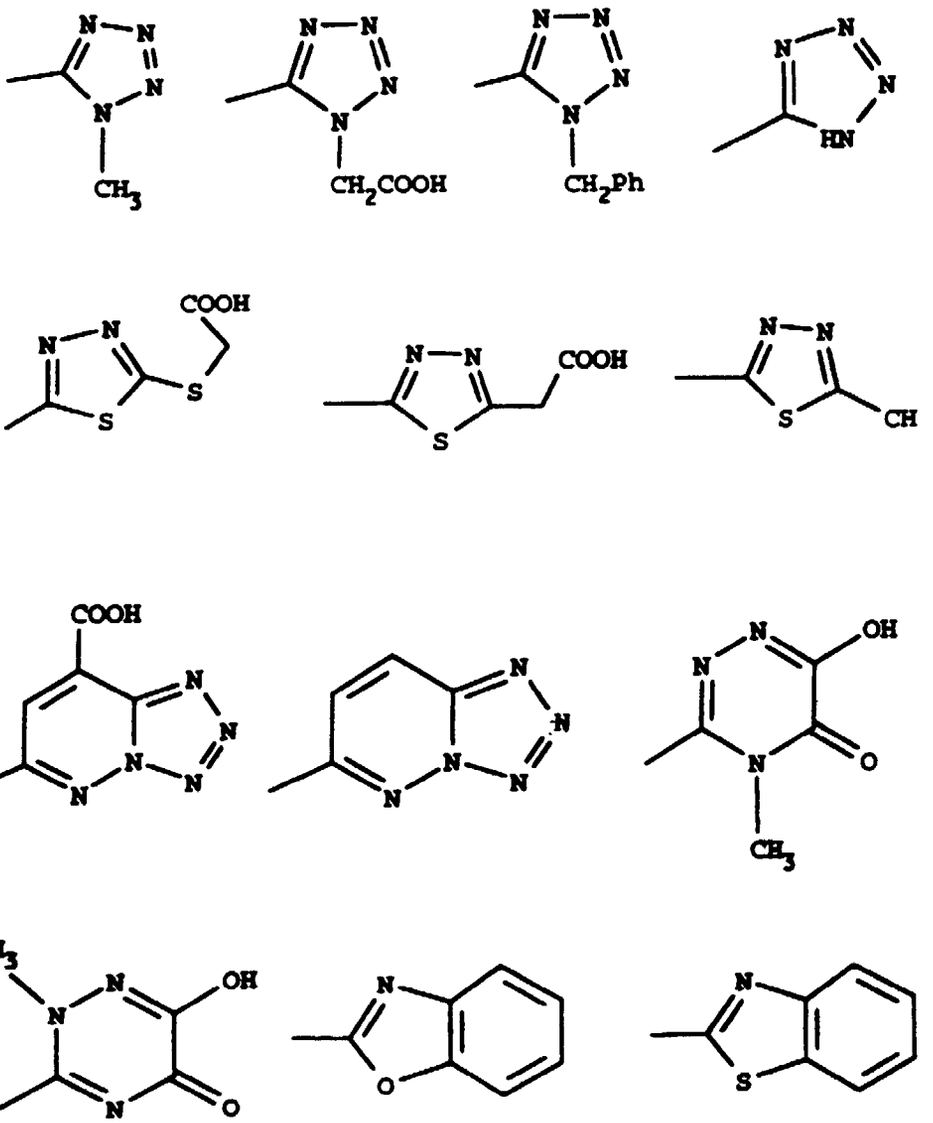
and the pharmaceutically and veterinarily acceptable salts thereof and all the possible isomers, e.g. stereoisomers, epimers, diastereoisomers, geometrical isomers, tautomers.

[0032] Still more preferred are compounds of formula (I') wherein n is two;

A is selected from tert-butyl, phenyl, 1-phenylethyl, 2-phenyl-2-propyl, 4-benzylphenyl, biphenylyl, naphthyl and tolyl, any of which is optionally substituted by a C_1-C_4 alkyl group or a carboxy group; B is

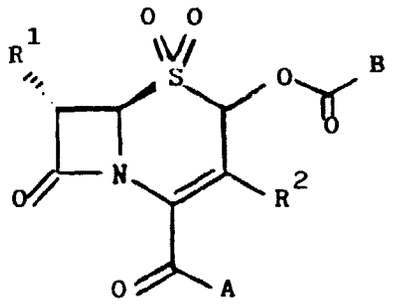
(1") methyl, ethyl, vinyl, propyl, allyl, isopropyl, n-butyl, s-butyl, tert-butyl, pentyl, optionally substituted by a group selected from carboxy, sulfo, amino, cyano, methoxy, phenoxy, naphthyloxy, p-chlorophenoxy, p-carboxyphenoxy;
(2") a phenyl group optionally substituted by one or two groups selected from fluoro, chloro, bromo, iodo, C_1-C_5 alkyl, methoxy, methylthio, methansulfonyl, carboxy, tert-butoxycarbonyl, benzhydryloxycarbonyl, carboxymethyl, sulfo, sulfomethyl, carboxymethylthio, carboxymethoxy, nitro, cyano, amino, dimethylamino, phenylamino, 2,3 dimethylphenylamino, dibutylamino, hydroxy, acetamido, trifluorocetamido, acetyl, trifluoroacetyl, carbamoyl and sulfamoyl;
(3") naphthyl, optionally substituted by one or two groups selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkyl, methoxy, methylthio, methansulfonyl, carboxy, tert-butoxycarbonyl, benzhydryloxycarbonyl, carboxymethyl, carboxymethylthio, carboxymethoxy, sulfo, sulfomethyl, nitro, cyano, amino, dimethylamino, hydroxy, acetamido, trifluorocetamido, acetyl, trifluoroacetyl, carbamoyl and sulfamoyl;
(4") anthryl or phenanthryl, optionally substituted by one or two groups selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkyl, methoxy, methylthio, methansulfonyl, carboxy, tert-butoxycarbonyl, benzhydryloxycarbonyl, carboxymethyl, carboxymethylthio, carboxymethoxy, sulfo, sulfomethyl, nitro, cyano, amino, dimethylamino, hydroxy, acetamido, trifluorocetamido, acetyl, trifluoroacetyl, carbamoyl and sulfamoyl;
(5") biphenyl -C_6H_4-C_6H_5, optionally substituted by a carboxy, sulfo, carboxymethyl or sulfomethyl group;
(6") a heterocycle chosen from thiazole, tetrazole, thiadiazole, triazole, isothiazole, oxazole, isoxazole, pyridine, pyrimidine, pyridazine, quinoline, isoquinoline, benzothiazole, benzoxazole, furane, thiophene, pyrrole, indole, chromane, benzofurane and benzothiophene either unsubstituted or substituted by one or two groups selected from fluoro, chloro, bromo, iodo, straight or branched C_1-C_4 alkyl, methoxy, methylthio, methanesulfonyl, carboxy, tert-butoxycarbonyl, benzhydryloxycarbonyl, carboxymethyl, carboxymethylthio, carboxymethoxy, sulfo, sulfomethyl, nitro, cyano, amino, dimethylamino, dimethylaminoethyl, hydroxy, acetamido, trifluorocetamido, acetyl, trifluoroacetyl, carbamoyl and sulfamoyl;
(7") phenyl substituted by t-butyl, N-carboxyphenylcarbamoyl, N-carboxybenzylcarbamoyl or N-carboxymethylphenylcarbamoyl or by methyl substituted by a group Y-A"', wherein Y is O, S or OCONH and A"' is tetrazole, thiadiazole, pyridine, triazole, C_1-C_4 alkyl, phenyl or benzyl either unsubstituted or substituted by one or two groups selected from C_1-C_4 alkyl, methansulfonyl, carboxy, sulfo, amino, hydroxy, oxo, acetamido, carboxymethyl and carboxymethylthio;
(8") phenyl(C_1-C_4)alkyl or naphthyl(C_1-C_4)alkyl, with yhe phenyl and naphthyl rings optionally substituted by C_1-C_5 alkyl, C_1-C_4 alkoxy, phenoxy, benzoyl, phenylamino, 2,6-dichlorophenylamino, phenyl, p-chlorophenyl, naphthyl, chloro, fluoro, hydroxy, carboxy, nitro, phthalimido, isoindolinyl, 1-oxoisoindolinyl.

R^1 is hydrogen or a chlorine, fluorine or bromine atom, or a methoxy, ethoxy, propoxy, isopropoxy, allyloxy, methylthio, ethylthio, isopropylthio, formamido, acetamido, trifluoroacetamido, chloroacetamido, methyl, ethyl, isopropyl, allyl or hydroxyethyl group;
R^2 is either hydrogen or methyl, chloromethyl, bromomethyl, methoxymethyl, carbamoyloxymethyl, carboxy, phenoxymethyl, 3-pyridyloxymethyl, acetoxymethyl, benzoyloxymethyl, p-carboxybenzoyloxymethyl, aminomethyl, pyridiniomethyl, glycyloxymethyl or a -CH_2-S-Het group wherein Het is a heterocyclic ring preferably chosen from



and the pharmaceutically and veterinarily acceptable salts thereof, and all the possible isomers including stereoisomers such as epimers, diastereoisomers, geometrical isomers, tautomers. Possible enolic forms of the above described compounds are to be considered tautomers of compounds of formula (I') and fall within the scope of the present invention.

[0033] Specific examples of the preferred compounds of the present invention are those listed in Table I.



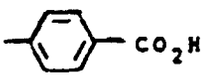
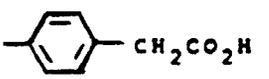
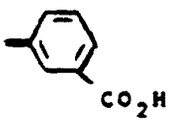
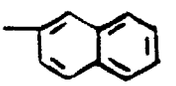
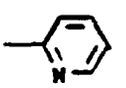
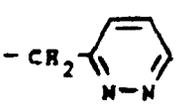
n	R^1	R^2	A	B
1	Cl	CH_3	t-Bu	Ph
2	CH_3O	CH_3	t-Bu	Ph
3	CH_3O	CH_3	t-Bu	
4	CH_3O	CH_3	t-Bu	
5	"	"	"	
6	"	"	"	CH_3
7	"	"	"	CH_2Ph
8	"	"	"	CH_2OPh
9	"	"	"	$CH_2CH_2CO_2H$
10	"	"	"	CH(OH)Ph
11	"	"	"	
12	"	"	"	
13	"	"	"	
14	"	"	"	

TABLE 1 continued

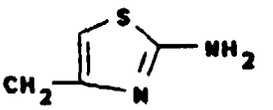
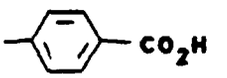
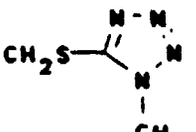
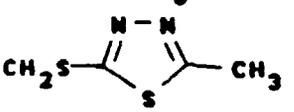
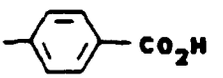
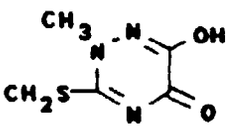
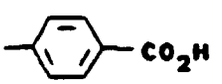
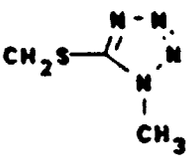
n	R^1	R^2	A	B
15	CH_3O	CH_3	t-Bu	
16	CH_3O	CH_2OCOCH_3	t-Bu	CH_3
17	CH_3O	CH_2OCOCH_3	t-Bu	Ph
18	CH_3O	CH_2OCOCH_3	t-Bu	
19	CH_3O		t-Bu	Ph
20	CH_3O		t-Bu	
21	CH_3O		t-Bu	CH_3
22	"	"	"	Ph
23	CH_3O	CH_3	Ph	CH_3
24	"	"	"	Ph
25	"	"	"	
26	"	CH_2OCOCH_3	"	Ph
27	"		"	Ph

TABLE 1 continued

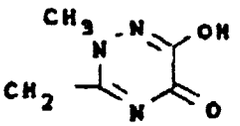
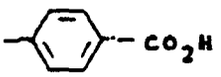
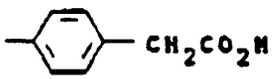
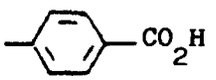
n	R^1	R^2	A	B
28	CH_3O		Ph	Ph
29	CH_3O	CH_3		Ph
30	CH_3O	CH_3		Ph
31	$CH=CH-CH_2$	CH_3	t-Bu	Ph
32	"	"	"	
33	"	"	Ph	Ph
34	"	"	"	"
35	CH_3CONH	"	"	"
36	CF_3CONH	"	"	"
37	HCONH	"	t-Bu	"

TABLE 1 continued

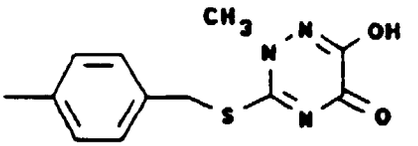
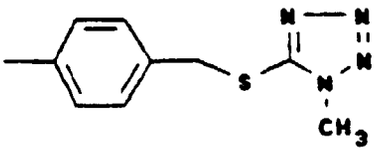
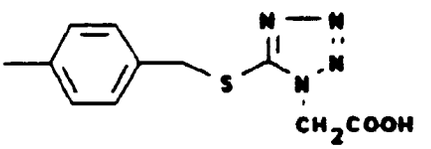
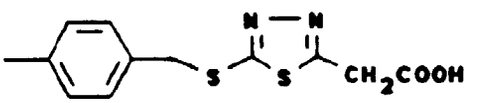
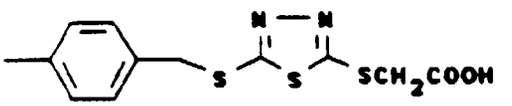
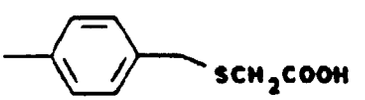
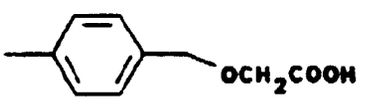
n	R^1	R^2	A	B
38	CH_3O	CH_3	t-Bu	
39	"	"	Ph	"
40	"	"	t-Bu	
41	"	"	Ph	"
42	"	"	t-Bu	
43	"	"	Ph	"
44	"	"	t-Bu	
45	"	"	Ph	"
46	"	"	t-Bu	
47	"	"	Ph	"
48	"	"	t-Bu	
49	"	"	Ph	"
50	"	"	t-Bu	
51	"	"	Ph	"

TABLE 1 continued

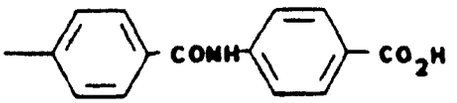
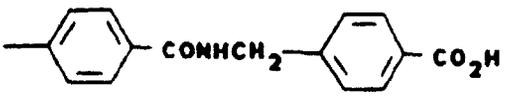
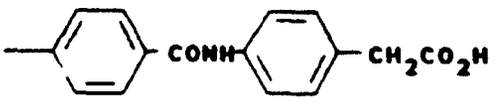
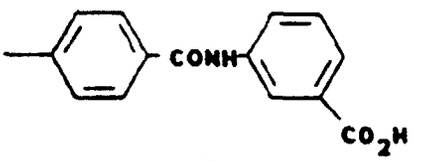
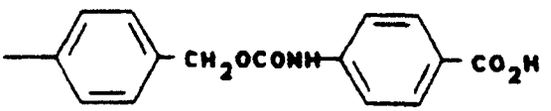
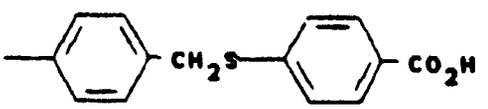
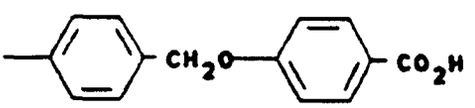
n	R^1	R^2	A	B
52	CH_3O	CH_3	t-Bu	
53	"	"	Ph	"
54	"	"	t-Bu	
55	"	"	Ph	"
56	"	"	t-Bu	
57	"	"	Ph	"
58	"	"	t-Bu	
59	"	"	Ph	"
60	"	"	t-Bu	
61	"	"	Ph	"
62	"	"	t-Bu	
63	"	"	Ph	"
64	"	"	t-Bu	
65	"	"	Ph	"

TABLE 1 continued

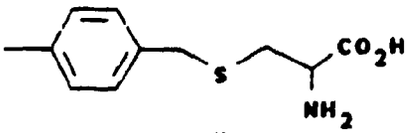
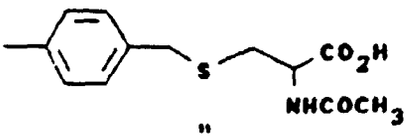
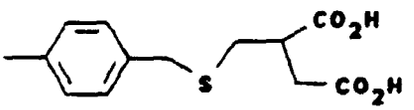
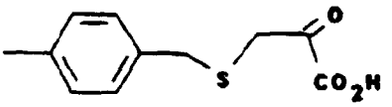
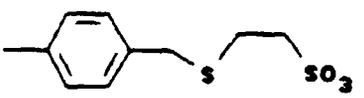
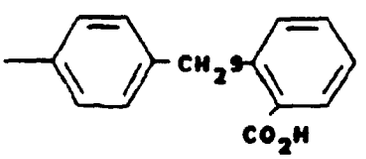
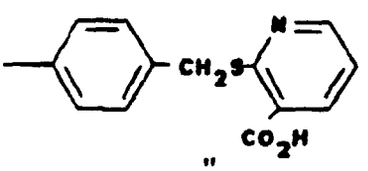
n	R^1	R^2	A	B
66	CH_3O	CH_3	t-Bu	
67	"	"	Ph	"
68	"	"	t-Bu	
69	"	"	Ph	"
70	"	"	t-Bu	
71	"	"	Ph	"
72	"	"	t-Bu	
73	"	"	Ph	"
74	"	"	t-Bu	
75	"	"	Ph	"
76	"	"	t-Bu	
77	"	"	Ph	"
78	"	"	t-Bu	
79	"	"	Ph	"

TABLE 1 continued

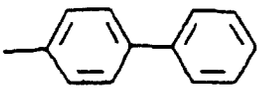
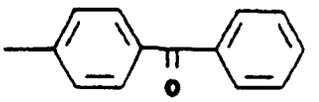
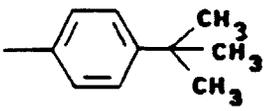
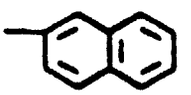
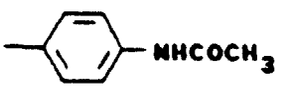
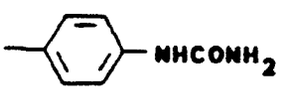
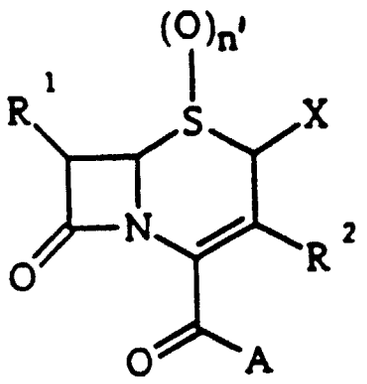
n	R^1	R^2	A	B
80	CH_3O	CH_3	t-Bu	H
81	"	"	t-Bu	
82	"	"	Ph	"
83	"	"	t-Bu	
84	"	"	Ph	"
85	"	"	t-Bu	
86	"	"	Ph	"
87	"	CH_2OCOPh	t-Bu	Ph
88	"	"	Ph	"
89	"	CH_3	Ph	
90	"	"	t-Bu	
91	"	"	Ph	"
92	"	"	t-Bu	
93	"	"	Ph	"

Table 1 continued

n	R^1	R^2	A	B
94	CH_3O	CH_3	t-Bu	$C(CH_3)_3$
95	"	"	Ph	"
96	"	"	t-Bu	$CH(C_2H_5)(CH_2)_3CH_3$
97	"	"	"	$CH_2NHCOPh$
98	"	"	"	CH_2CH_2COPh
99	"	"	"	$-C_6H_5-4-SO_3H$
100	"	"	Ph	"
101	"	"	"	$-C_6H_5-4-CH_2SO_3H$
102	"	"	t-Bu	"

[0034] The present invention also provides a process for the preparation of cephem sulphones of formula (I), which process comprises:

(i) reacting a compound of formula (II)



(II)

wherein either

(i_a) n' is 0, 1 or 2; A, R^1 and R^2 are as defined above, and X is a leaving group, with a compound of formula (III)

B-C(O)O-M (III)

wherein B is as defined above and M is hydrogen or a metal; or
(i_b) n', A, R^1 and R^2 are as defined above, and X is hydrogen, with a compound of formula (IV)

B-C(O)O-O-W-B' (IV)

wherein B is as defined above and B', being the same or different is as defined above for B and W is either a bond or a group selected from -C(O)-, -C(O)C-, -$S(O)_2$-, -C(O)NR^v- wherein R^v is phenyl or a C_1-C_4 alkyl group;
(ii) if needed, when n in the compound of formula (I) is of higher value than n' in formula II as above defined, oxidizing the obtained compound to a compound of formula (I); and
(iii) if desired, converting the resulting compound of formula (I) into a pharmaceutically or veterinarily acceptable salt thereof, and/or, if desired, converting the compound or salt into a stereoisomer, e.g. epimer, diastereoisomer, geometrical isomer or tautomer thereof.

[0035] In step (i_a) the leaving group X is typically a halogen, preferably bromine, chlorine or iodine. When M in formula (III) is hydrogen the acyloxylation reaction is usually performed in the presence of an inorganic or organic base. These external bases are generally not required when M of formula (III) is a metal, e.g an alkaline metal or a heavy metal, preferably a halophylic metal such as silver, copper, mercury or lead. The reaction (i_a) can be carried out in a wide range of organic solvents such as acetonitrile, N,N-dimethylformamide, dichloromethane, tetrahydrofuran, dioxane, ethyl acetate, chloroform, benzene, carbon tetrachloride, diethyl ether, dimethoxyethane, sulpholane, dimethylsulphoxide, hexamethylphosphoramide, N-methyl pyrrolidone, acetone, water and mixtures of any of these. Reaction temperatures range between -50°C and +120°C, preferably between -20°C and +80°C. Preferred external bases are tertiary organic bases either aliphatic or aromatic or alicyclic such as triethylamine, diisopropylethylamine, aniline, pyridine, lutidine, collidine, quinoline, N-methylmorpholine, N-methylpyrrolidine, diazabicyclooctane (DABCO); or inorganic bases such as alkaline bicarbonates, or carbonates, e.g. sodium bicarbonate, calcium carbonate, cesium carbonate, potassium carbonate. A beneficial effect has often been observed upon addition of alkaline metal salts such as sodium iodide or potassium iodide and additives such as molecular sieves, alumina or calcium oxide. The reaction can also be carried out in the presence of heavy metal salts such as silver nitrate, silver perchlorate, silver triflate, copper nitrate, mercury nitrate.

[0036] Step (i_b) is usually performed in the presence of tertiary aliphatic or aromatic organic bases such as 1,5-diazabicyclo[4,3,0]non-5-ene, 1,8-diazabicyclo[5,4,0]undec-7-ene, 1,1,3,3-tetramethylguanidine, 1,4-diazabicyclo [2,2,2]octane, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, triethylamine, pyridine, lutidine, collidine, quinoline. The reaction can be carried out in a wide range of non-protic organic solvents such as acetonitrile, N,N-dimethylformamide, tetrahydrofuran, dioxane, benzene, sulpholane, N,N-dimethylacetamide, hexamethylphosphoramide, N-methyl pyrrolidone or mixtures thereof. Temperatures for reaction (i_b) range between -60°C and +40°C, preferably between -30°C and room temperature.

[0037] If needed, the oxidation reaction mentioned in step (ii) is performed with organic or inorganic peracids or salts thereof, preferably peracetic acid, metachloroperbenzoic acid, permaleic acid, perphthalic acid, oxone, sodium or potassium persulphate in suitable organic solvents or mixtures of organic solvents with water. Preferred reaction temperatures range between -40°C and +40°C.

[0038] It is understood that in the process above any functional group, if needed or desired can be masked by a conventional method and unmasked at the end or when convenient. It is also understood that the groups R^1, R^2, A and B can be converted by conventional methods into different groups included within those previously defined, if desired, at the end or at any stage of the process above. This conversion or masking/unmasking of the protecting groups are well known in the cephalosporin area (see, e.g. "Cephalosporins and Penicillins", E.H. Flynn Ed.).

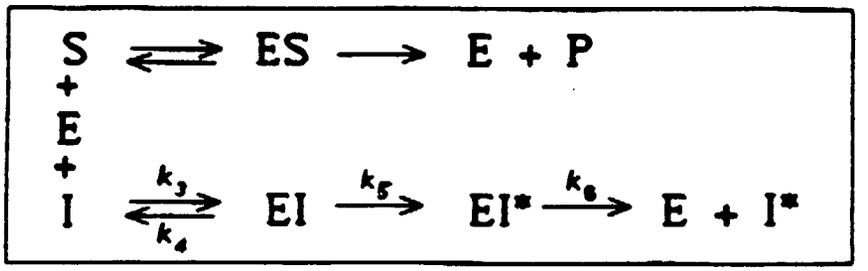
[0039] Compounds of formula (II) are known or can be prepared from known compounds as described in EP-A-0337704. Compounds of formulae (III) and (IV) are known compounds or can be prepared from known compounds by known methods.

[0040] The potential of protease inhibitor therapy in the treatment of conditions resulting from the destruction of connective tissues has recently received particular attention. Much effort has been devoted to the search for inhibitors of human leucocyte elastase (HLE), which is the primary destructive agent in pulmonary emphysema and is probably involved in rheumatoid arthritis (J.C. Power, Am. Rev. Resp. Diseases 127, S54-S58, 1983; C.H. Hassal et al, FEBS Letters, 183, n. 2, 201, 1985, G. Weinbaum and V.V. Damiano, TIPS, 8, 6, 1987; M. Velvart, Rheumatol. Int. 1, 121, 1981). Low molecular weight inhibitors appear to have a number of advantages over natural high molecular weight protease inhibitors from either plant or animal sources: 1) they can be obtained in quantities; 2) they can be rationally designed or optimised; 3) they are not antigenic; and 4) they may be used orally or in aerosols. Many low molecular weight elastase inhibitors discovered so far contain reactive functional groups (chloromethyl ketones, isocyanates, etc); they may react with functional groups of proteins, and therefore they may be quite toxic. In this respect, β-lactam

compounds are of potential interest because, though reactive towards serine protease, they are, as it is known, non-toxic at very high concentrations.

[0041] The compounds of the present invention are characterized by high inhibitory activity on elastases, especially human leucocyte elastase (HLE). In particular, the introduction of the acyloxy group O-C(O)-B, wherein B is as above described, at the C-2 position of the cephem nucleus, resulted in an unpredictable enhancement of inhibitory activity, relative to the corresponding C-2 unsubstituted compounds (formula (II)), which are disclosed in US patent US-A-5,077,286 (Dec. 31,1991), while retaining good chemical stability.

[0042] When tested as inhibitors of human leucocyte elastase (HLE), compounds of formula (I) showed high "potency" (low value of apparent dissociation constant of HLE-inhibitors complex at steady rate K_i^{SS}) and high "efficiency" (high rate of formation of the HLE-inhibitor complex, K_5/K_i):



$$K_I = k_4/k_3 \qquad K_I^{ss} = K_I \frac{k_6}{(k_5 + k_6)}$$

wherein

E=enzyme (HLE)
S=substrate (see Protocol)
P=product (see Protocol)
I=inhibition
EI=Michaelis complex
EI*=covalent complex (inactivated enzyme)
I*=inactivated inhibitor

[0043] To illustrate this point, Table 2 reports such parameters for a representative compound within the present invention (compound No.2 in Table 1), in comparison with the corresponding compound of formula (II) lacking the acyloxy group at the C-2 position. Table 2 incorporates, as a meaningful reference, the corresponding data obtained for L-659,286, another β-lactam compound which was recently reported to undergo preclinical studies for the treatment and control of pulmonary emphysema (Am. Rev. Respir. Dis. 1988, 137, 204; Agents and Actions, 1988, 25, 60; Journal of Cellular Biochemistry 1989, 39, 47-53; J.Med.Chem. 1992, 35 3731-3744, compound 11f, in text and tables), which was independently synthesized in our laboratories.

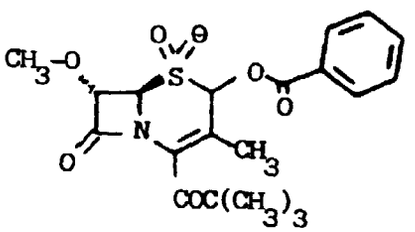
In addition, Table 3 reports the corresponding data for other compounds of the present invention, showing that excellent or superb potency is in general a common feature of this novel class of cephem derivatives. As a matter of fact, inhibition parameters were sometimes outside the determination limits of our experimental protocol (K_i^{SS} less than 2 nanomolar, K_5/K_I more than 2,000,000 $M^{-1}sec^{-1}$).

TABLE 2

Kinetic parameters for HLE-inhibition (see Protocol below) by a representative compound of the present invention (Compound No. 2 in Table I), the corresponding previous art compound, and a reference cephem sulphone selected as a particularly interesting HLE inhibitor (Merck S & D)

Compound	Potency K_i^{app}(nM)	"Efficacy" K_5/K_i($M^{-1}s^{-1}$)
Present invention[1]	< 2	$1.5\ 10^6$
Previous art[2]	1300	$0.6\ 10^2$
Reference	75	$9.2.10^3$

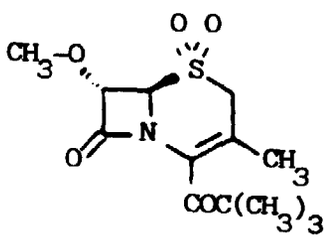
1) Structure



FCE 28204

(Table 1, Compound No.2)

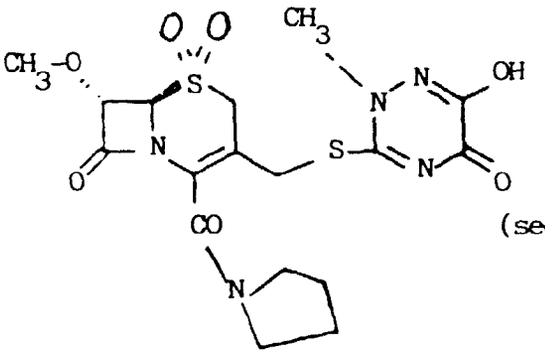
2) Structure



FCE 25580

(Compd. in US Pat. 5,077,286, Example 2)

3) Structure



Merck S&D

L-659,286

(see above for reference)

TABLE 3

Kinetic parameters for HLE inhibitors (see Protocol below) by some representative compounds of the present invention		
Compound #	"Potency" K_i^{ss}(nM)	"Efficacy" K_5/K_I ($M^{-1}sec^{-1}$)
6	4	$6.5\ 10^4$
11	<2*	$>2^*\ 10^6$
19	<2*	$>2^*\ 10^6$
24	8	ND
25	29	$3.4\ 10^4$
38	<2*	$7.0\ 10^5$
80	600	$1.4\ 10^3$
83	2	$5.0\ 10^5$
87	<2*	$1.6\ 10^6$
94	<2*	$1.5\ 10^6$
96	<2*	$>2^*\ 10^6$
98	<2*	$3.0\ 10^5$

(*) Values outside the determination limits allowed by the experimental protocol

ND: Not determined

Protocol

[0044] Kinetic parameters of HLE (Calbiochem) were determined at 37°C, 0.027M pH 7.4 phosphate buffer, 1% DMSO, 1% MeCN, NaCl (I=0.15), by monitoring the release of 7-amino-4-methylcoumarin (fluorescence detection) from N-methoxysuccinyl-alanyl-prolyl-valyl-7-amido-4-methylcoumarin as the substrate, according to the equations:

$$[P]=V_s t+\frac{V_z-V_s}{K}(1-e^{kt})$$

$$K=K_6+K_5\frac{[I]/K_I}{1-[S]/K_m+[I]/K_I}$$

$$V_s=V_o\frac{1+[S]/K_m}{1+[S]/K_m+[I]/K_i^{SS}}$$

wherein

[P], [I], [S]=product, inhibitor, and substrate concentration

V_s=steady state rate
V_z=zero time rate
V_o=rate at [I]=0
K_m=Michaelis constant for the enzyme substrate pair (independently determined under the same experimental conditions). Full details of the Experimental Protocol are reported in M. Alpegiani et al., Eur. J. Med. Chem. 1992, 27, 875-890.

The compounds of formula (I) and their salts have high elastase-inhibiting activity and quite negligible toxicity (the orientative acute toxicity by i.v., oral or aerosol route is almost always greater than 500 mg/kg in rat). A patient is treated according to the present invention by a method comprising administering to the patient a therapeutically effective amount of a compound of formula (I) or a salt thereof. In this way the compounds and salts of the present invention can be used in the treatment of inflammatory and degenerative diseases caused by proteolytic enzymes in mammals including humans. For example, the compounds and their salts can be used to prevent or arrest the progression of diseases caused by proteolytic degradation of lungs and connective tissues, reduce inflammation and fever, and relieve pain. Such diseases are emphysema, acute respiratory distress syndrome, bronchial inflammation, rheumatoid arthritis, osteoarthritis, infectious arthritis, rheumatic fever, spondylitis, gout, lupus, psoriasis, and the like. The condition of the patient may thus be improved.

[0045] The present invention also provides a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, for use as an elastase inhibitor. The invention further provides pharmaceutical and veterinary compositions containing a suitable carrier and/or diluent and, as an active principle, a 2-acyloxycephem sulphone of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof. The pharmaceutical or veterinary compositions containing a compound of formula I or salt thereof may be prepared in a conventional way by employing conventional non-toxic pharmaceutical carriers or diluents in a variety of dosage forms and ways of administration.

[0046] The compounds of formula I can be administered:

A) Orally, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Formulation for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy propylmethylcellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, or one or more sweetening agents, such as sucrose or saccharin. Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or

wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present. The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents.

B) Parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or olagenous suspension.

This suspension may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables;

C) By inhalation, in the form of aerosols or solutions for nebulizers;

D) Rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols;

E) Topically, in the form of creams ointments, jellies, solutions or suspensions.

[0047] The present invention further provides a method for controlling inflammatory and degenerative diseases by administering a therapeutically effective amount of one or more of the active compounds of formula I, or a pharmaceutically or veterinarily acceptable ssalt thereof, to humans or mammalians in need of such treatment.

[0048] Daily doses are in the range of about 0.1 to about 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease, and the frequency and route of administration; preferably, daily dosage levels for humans are in the range of 20 mg to 2 g. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, for example his or her age, weight and condition, and the particular mode of administration. For example, a formulation intended for the oral administration to humans, may contain from 5 mg to 2 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500mg of active ingredient.

[0049] The following examples further illustrate the invention.

EXAMPLE 1

2-Benzoyloxy-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide

[0050] **Method A.** 2-Bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (114 mg) was dissolved in dry acetonitrile (4 ml) and treated with silver benzoate (120 mg). After stirring for 30 minutes at room temperature, the reaction mixture was partitioned between EtOAc and water. Following drying over Na_2SO_4, the organic phase was rotoevaporated. The residue was passed through a silica gel column eluting with n-hexane/EtOAc mixtures. The title product was obtained as a white solid (85 mg).

NMR ($CDCl_3$, 200 MHz) 1.30 (9H,s); 1.76 (3H,s); 3.57 (3H,s); 4.88 (1H,d,J=1.8Hz); 5.20 (1H,d,J=1.8Hz); 5.92 (1H,s); 7.4-7.8 (5H,m).

IR (KBr) 1795, 1755, 1700.

Method B. 1,5-Diazabicyclo[5,4,0]non-5-ene (0.13 ml) was added dropwise in 5 minutes to a mixture of 4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (301 mg) and benzoyl peroxide (242 mg) in dry acetonitrile (8 ml) under a nitrogen blanket while keeping the temperature at -5° C. After stirring for 20 minutes at 0°C, the reaction mixture was poured into EtOAc/water. The upper layer was dried (Na_2SO_4) and concentrated *under vacuum.* Flash chromatography of the residue allowed the isolation of unreacted starting material (120 mg) and gave the title product

as a white powder (70 mg).

EXAMPLE 2

2-Acetoxy-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 6)

[0051] A mixture of 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (100 mg) and silver acetate (50 mg) in acetonitrile (4 ml) was stirred at room temperature for 1 hour. After partitioning between EtOAc and water, the organic layer was dried (Na_2SO_4) then rotoevaporated. The residue was purified by flash chromatography (eluting with n-hexane/EtOAc mixtures) affording the title product as a waxy solid (76 mg).

NMR ($CDCl_3$, 200 MHz) 1.26 (9H,s); 1.68 (3H,s); 2.24 (3H,s); 3.54 (3H,s); 4.72 (1H,d,J-1.8Hz); 5.15 (1H,d,J-1.8Hz); 5.69 (1H,s).

EXAMPLE 3

[0052] Following the procedure described in Example 2 and using the suitable silver carboxylate the following products were obtained:

2-[4-(Benzoyl)benzoyloxy]-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 83)

[0053] NMR ($CDCl_3$, 200 MHz) 1.30 (9H,s); 1.77 (3H,s); 3.58 (3H,s); 4.87 (1H,d,J=8Hz); 5.21 (1H,d,J=1.8Hz), 5.94 (1H,s); 7.4-7.9 (5H,m); 7.90 (2H,d,J=8.4Hz); 8.19 (2h,d,J=8.4Hz)
[0054] IR (KBr) 1800, 1750, 1705, 1760.

4-tert-Butylcarbonyl-7α-methoxy-3-methyl-2-[(β-naphthyl)oxy]-3-cephem 1,1-dioxide (compound 11)

[0055] NMR ($CDCl_3$, 200 MHz) 1.30 (9H,s); 1.79 (3H,s); 3.58 (3H,s); 4.93 (1H,d,J=1.7Hz); 5.22 (1H,d,J=1.7Hz); 5.97 (1H,s); 7.5-8.2 (7H,m)
IR (KBr) 1790, 1740, 1700

4-tert-Butylcarbonyl-2-formyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 80)

[0056] NMR ($CDCl_3$, 200 MHz) 1.28 (9H,s); 1.72 (3H,s); 3.56 (3H,s); 4.78 (1H,d,J=8Hz); 5.19 (1H,d,J=1.8Hz); 5.80 (1H,br.s); 8.23 (1H,d,J=0.9Hz)
IR (KBr) 1795, 1755, 1700

EXAMPLE 4

4-tert-Butylcarbonyl-2-{4-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]benzoyloxy} -7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 38)

[0057] A solution of 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (110 mg) in acetonitrile (100 ml) was treated with 4-[(6-benzhydryloxy-2,5-dihydro-2-methyl-5-oxo-1,2,4- triazin-3-yl)thiomethyl]benzoic acid siver salt (230 mg). The reaction mixture was stirred at room temperature for 30 minutes, then diluted with EtOAC, filtered and rotoevaporated. Upon purification of the residue by flash chromatography 4-tert-butylcarbonyl-2-{4-[(6-benzhydryloxy-2,5-dihydro-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl] benzoyloxy}-7α-methoxy-3-methyl-3-cephem 1,1-dioxide was obtained as a white solid (mg 75). This product was dissolved in methylene chloride (0.5 ml) and sequentially treated with anisole (0.03 ml) and trifluoroacetic acid (0.5 ml).
[0058] After stirring 30 minutes at room temperature, the solution was concentrated *under vacuum.* Addition of diisopropyl ether to the residue caused the formation of a whitish solid, which was filtered and dried *in vacuo* (40 mg) corresponding to the title product.
IR (KBr) 1800, 1745, 1705.

EXAMPLE 5

2-Benzoyloxy-7α-methoxy-3-methyl-4-phenylcarbonyl-3-cephem 1,1-dioxide (compound 24)

[0059] A mixture of 2-bromo-7α-methoxy-3-methyl-4-phenylcarbonyl-3-cephem 1,1-dioxide (130 mg) and silver ben-

zoate (115 mg) in acetonitrile (10 ml) was stirred at room temperature for 30 minutes. The reaction mixture was diluted with EtOAc, then filtered and the filtrate was rotoevaporated. The residue was purified by flash chromatography (eluting with n-hexane/EtOAc mixtures) affording the title product as a white powder (85 mg) IR (KBr) 1805, 1740, 1675.
NMR ($CDCl_3$, 200 MHz) 1.72 (3H,s); 3.55 (3H,s); 4.97 (1H,d,J=1.8Hz); 5.24 (1H,d,J=1.8Hz); 6.10 (lH,s); 7.4-8.2 (10H, m).

EXAMPLE 6

2-Benzoyloxy-3-benzoyloxymethyl-4-tert-butylcarbonyl-7α-methoxy-3-methyl-2(4-phenyl)benzoyloxy-3-cephem 1,1-dioxide (compound 87)

[0060] A mixture of 2-bromo-3-bromomethyl-4-tert-butylcarbonyl-7α-methoxy-3-cephem 1,1-dioxide (225 mg) and silver benzoate (350 mg) in acetonitrile (10 ml) was stirred at room temperature for 2 hours. After partitioning between EtOAc and water, the upper layer was dried (Na_2SO_4) and rotoevaporated. The residue was purified by flash chromatography (eluting with n-hexane/EtOAc mixtures) affording the title product as a white powder (90 mg) IR (KBr) 1800, 1755, 1740, 1700 (sh).
NMR ($CDCl_3$, 200 MHz) 1.36 (9H,s); 3.59 (3H,s); 4.73 (1H,d,J=13.5Hz); 4.80 (1H,d,J=13.5Hz); 4.99 (1H,d,J=2.1Hz); 5.13 (1H,d,J=2.1Hz); 6.26 (1H,s); 7.2-8.2 (10H,m)

EXAMPLE 7

4-tert-Butylcarbonyl-7α-methoxy-3-methyl-2-pivaloyloxy-3-cephem 1,1-dioxide (compound 94)

[0061] Starting from 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide and silver pivalate, and following the procedure described in Example 2, the title product was obtained as a white powder.
IR (KBr) ν_{max} 1795, 1765, 1705 cm^{-1}.
NMR ($CDCl_3$) δ 1.27 (9H, s), 1.29 (9H, s), 1.67 (3H, s), 3.56 (3H, s), 4.70 (1H, d, J= 1.8 Hz), 5.16 (1H, d, J= 1.8 Hz), 5.67 (1H, s).
FAB-MS 402 (MH^+).

EXAMPLE 8

4-Benzoyl-7α-methoxy-3-methyl-2-pivaloyloxy-3-cephem 1,1-dioxide (compound 95)

[0062] Starting from 4-benzoyl-2-bromo-7α-methoxy-3-methyl-3-cephem 1,1-dioxide and silver pivalate, and following the procedure described in Example 2, the title product was obtained as a white powder.
IR (KBr) ν_{max} 1790-1770, 1760, 1680 cm^{-1}.
NMR ($CDCl_3$) δ 1.31 (9H, s), 1.63 (3H, s), 3.54 (3H, s), 4.79 (1H, d, J= 1.9 Hz), 5.20 (1H, d, J= 1.9 Hz), 5.85 (1H, s), 7.4-8.0 (5H, m).
FAB-MS 422 (MH^+).

EXAMPLE 9

4-tert-Butylcarbonyl-2-(2-ethylhexanoyl)oxy-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 96)

[0063] Starting from 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide and silver 2-ethylhexanoate, and following the procedure described in Example 2, the title product was obtained as a white powder.
IR ($CHCl_3$) ν_{max} 1800, 1760, 1705 cm^{-1}.

EXAMPLE 10

4-tert-Butylcarbonyl-2-hippuroyloxy-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 97)

[0064] Starting from 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide and hippuric acid silver salt, and following the procedure described in Example 2, the title product was obtained as a whitish foam.
IR (KBr) ν_{max} 1790, 1700, 1655 cm^{-1}.
NMR ($CDCl_3$) δ 1.27 (9H, s), 1.75 (3H, s), 3.55 (3H, s), 4.29 (1H, dd, J= 4.9 and 18.3 Hz), 4.52 (1H, dd, J= 6.1 and 18.3 Hz), 4.76 (1H, d, J= 1.5 Hz), 5.18 (1H, d, J= 1.5 Hz), 5.76 (1H, s), 6.76 (1H, m, exch. D_2O), 7.4-8.0 (5H, m).

EXAMPLE 11

2-[3-(Benzoyl)propionyl]oxy-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide. (compound 98)

[0065] Starting from 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide and 3-(benzoyl)propionic acid silver salt, and following the procedure described in Example 2, the title product was obtained as a white powder.
IR (KBr) ν_{max} 1775, 1705, 1690 cm^{-1}.
NMR ($CDCl_3$) δ 1.25 (9H, s), 1.78 (3H, s), 2.9-3.0 (2H, m), 3.3-3.5 (2H, m), 3.55 (3H, s), 4.76 (1H, d, J= 1.5 Hz), 5.17 (1H, d, J= 1.5 Hz), 5.70 (1H, s), 7.4-8.1 (5H, m).

EXAMPLE 12

2-Benzoyloxy-4-tert-butylcarbonyl-7α-methoxy-3-(1-methyl--1,2,3,4-tetrazol-5-yl)thiomethyl-3-cephem 1,1-dioxide (compound 19)

[0066] To a solution of 4-tert-butylcarbonyl-7α-methoxy-3-(1-methyl-1,2,3,4-tetrazol-5-yl)thiomethyl-3-cephem 1,1 dioxide (350 mg) in dichloromethane (30 ml), N-bromosuccinimide (200 mg) and triethylamine (0.13 ml) were added sequentially. The mixture was stirred for 15 min at room temperature. Following dilution with dichloromethane, the organic phase was sequentially washed with 4% aqueous $NaHSO_3$, saturated $NaHCO_3$ and water. After drying over Na_2SO_4 and removal of the solvent, the residue was purified by flash chromatography (eluting with hexane-EtOAc mixtures) affording 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-(1-methyl-1,2,3,4-tetrazol-5-yl) thiomethyl-3-cephem 1,1-dioxide as a waxy solid (200 mg), IR (KBr) ν_{max} 1800, 1700 cm^{-1}. A portion of this material (180 mg) was dissolved in acetonitrile (10 ml) and treated with silver benzoate (95 mg). The mixture was stirred for 30 min at room temperature, then filtered and rotoevaporated. Following flash chromatography (eluting with gradient of EtOAc in hexane) the title product was obtained as a light yellow solid (80 mg).
IR (KBr) νmax 1805, 1750, 1700 cm^{-1}.
NMR ($CDCl_3$) δ 1.35 (9H, s), 3.59 (3H, s), 3.84 (3H, s), 3.87 and 4.19 (2H, each d, J= 14.2 Hz), 4.99 (1H, d, J= 1.9 Hz), 5.24 (1H, d, J= 1.9 Hz), 6.25 (1H, s), 7.3-8.1 (5H, m).

EXAMPLE 13

4-tert-Butylcarbonyl-2-(4-carboxybenzoyl)oxy-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 3)

[0067] A solution of 2-bromo-4-tert-butylcarbonyl-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (110 mg) in acetonitrile (200 mg) was treated with 4-(p-methoxybenzyloxycarbonyl)benzoic acid silver salt (200 mg). The resulting mixture was stirred for 5 hours at room temperature, then diluted with EtOAc, filtered, and sequentially washed with water, aqueous $NaHCO_3$ and brine. After drying over Na_2SO_4, the organic layer was concentrated to dryness. The oily residue was dissolved in dichloromethane (3 ml) and treated with anisole (0.1 ml) and trifluoroacetic acid (1 ml). After standing for 2 hours at r.t., the solvent was removed under reduced pressure and the residue was chromatographed over silica gel (eluting with gradient of EtOAc in hexane). The title product was obtained as a white solid (55 mg).
IR (KBr) ν_{max} 3500-2500, 1805, 1745, 1705 cm^{-1}.
NMR ($CDCl_3$) δ 1.31 (9H, s), 1.77 (3H, s), 3.58 (3H, s), 4.86 (1H, d, J= 1.5 Hz), 5.21 (1H, d, J= 1.5 Hz), 5.93 (1H, s), 8.0-8.2 (4H, m).

EXAMPLE 14

4-Benzoyl-2-(4-carboxybenzoyl)oxy-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (compound 25)

[0068] Starting from 4-benzoyl-2-bromo-7α-methoxy-3-methyl-3-cephem 1,1-dioxide (110 mg) and 4-(p-methoxybenzyloxycarbonyl)benzoic acid silver salt (200 mg), and following the procedure described in Example 13, the title product was obtained as a white powder.
IR (KBr) ν_{max} 3500-2500, 1805, 1740, 1680 cm^{-1}.
NMR ($CDCl_3$) δ 1.72 (3H, s), 3.55 (3H, s), 4.96 (1H, d, J= 1.7 Hz), 5.25 (1H, d, J= 1.5 Hz), 6.11 (1H, s), 7.4-8.4 (9H, m).

EXAMPLE 15

4-Benzoyl-2-benzoyloxy-3-benzoyloxymethyl-7α-methoxy-3-cephem 1,1-dioxide (compound 88)

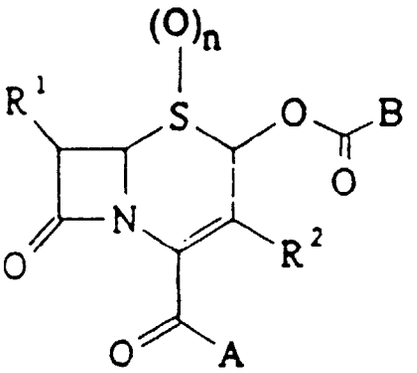
[0069] Starting from 4-benzoyl-2-bromo-3-bromomethyl-7α-methoxy-3-cephem 1,1-dioxide and silver benzoate, and following the procedure described in Example 6 the title product was obtained as a white powder.
IR (KBr) ν_{max} 1810, 1745, 1680 cm^{-1}.
NMR ($CDCl_3$) δ 3.56 (3H, s), 3.81 (1H, d, J= 11.9 Hz), 3.93 (1H, d, J= 11.9 Hz), 5.10 (1H, d, J= 1.6 Hz), 5.22 (1H, d, J= 1.6 Hz), 6.53 (1H, s), 7.4-8.2 (15H, m).

GENERAL PROCEDURE FOR PREPARING SILVER CARBOXYLATES

[0070] A mixture of the proper carboxylic acid (10 mmol) in water (50 mL) was treated with sodium methoxide (0.54 g, 10 mmol) and stirred until a clear solution appeared. Silver nitrate (1.7 g, 10 mmol) was then added in the dark, causing the immediate formation of a white precipitate. After stirring for few minutes, the mixture was filtered and the solid was sequentially washed with water and ethyl ether. Following drying in an oven at 55 °C under vacuum, silver carboxylates were obtained as whitish or light grey powders in yields ranging from 60% to 95%.

Claims

1. A compound of the formula (I), or a pharmaceutically or veterinarily acceptable salt thereof;



(I)

wherein n is one or two:

A and B are each, independently, hydrogen or an organic radical selected from optionally substituted C_1-C_{12} straight or branched alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_6-C_{14} aryl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, or C_7-C_{18} aralkyl, C_8-C_{18} aralkenyl, C_8-C_{18} aralkynyl, (cycloalkyl)alkyl, (cycloalkyl)alkenyl, heterocyclyl, (heterocyclyl)alkyl and (heterocyclyl)alkenyl groups;
when present, the substituents are selected from:

- halo
- hydroxy;
- nitro;
- azido;
- mercapto
- amino (i.e., $-NH_2$, or $-NHR^i$ or $-NR^iR^{ii}$) wherein R^i and R^{ii}, which are the same or different, are C_1-C_{12} straight or branched alkyl or phenyl or benzyl; or phenyl carboxy groups;
- formyl
- cyano;
- carboxy(alkyl) (i.e., $(CH_2)_tCOOH$ or $(CH_2)_tCOOR^i$) wherein R^i is as defined above and t is 0, 1, 2 or 3;
- sulfo
- acyl (i.e., $-C(O)R^i$) wherein R^i is as defined above or trifluoroacetyl

- carbamoyl ; N-methylcarbamoyl or N-carboxymethylcarbamoyl
- carbamoyloxy
- acyloxy (i.e., -OC(O)R^i) wherein R^i is as defined above or formyloxy
- alkoxycarbonyl or benzyloxycarbonyl (i.e., -C(O)OR^i) wherein R^i is as defined above;
- alkoxycarbonyloxy or benzyloxycarbonyloxy (i.e., -OC(O)OR^i) wherein R^i is as defined above;
- alkoxy, phenoxy or benzyloxy (i.e., -OR^i) wherein R^i is as defined above;
- alkylthio, phenylthio or benzylthio (i.e., -SR^i) wherein R^i is as defined above;
- alkylsulfinyl, phenylsulfinyl or benzylsulfinyl (i.e., -S(O)R^i) wherein R' is as defined above;
- alkylsulfonyl, phenylsulfonyl or benzylsulfonyl (i.e., -$S(O)_2R^i$) wherein R^i is as defined above;
- acylamino (i.e., -NHC(O)R^{iii} or -NHC(O)OR^{iii}) wherein R^{iii} is C_1-C_{12} straight or branched alkyl, phenyl, benzyl, CH_2CH_2COOH or $CH_2CH_2CH_2COOH$;
- sulfonamido (i.e., -$NHSO_2R^i$) wherein R^i is as defined above;
- guanidino (i.e., -NHC(=NH)NH_2);
- C_1-C_4 alkyl, C_2-C_4 alkenyl or alkynyl;
- C_3-C_6 cycloalkyl;
- substituted methyl selected from chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, aminomethyl, N,N-dimethylaminomethyl, azidomethyl, cyanomethyl, carboxymethyl, sulfomethyl, carbamoylmethyl, carbamoyloxymethyl, hydroxymethyl, C_1-C_4 alkyloxycarbonylmethyl, guanidinomethyl.
- phtalimido, indolyl, indolinyl, isoindolinyl, 1-oxoisoindolinyl;

R^1 represents

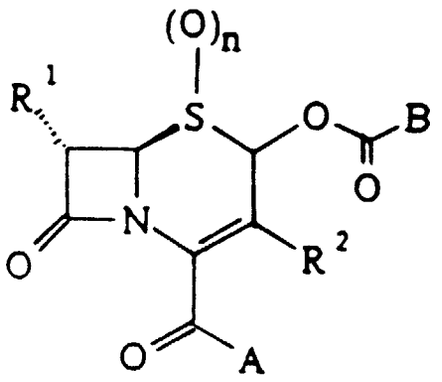
(1) a chlorine, fluorine, bromine or iodine atom
(2) A as defined above
(3) an ether OA wherein A is as defined above
(4) a thioether, sulphoxide or sulphone -$S(O)_m$A wherein m is either zero, one or two and A is as defined above;
(5) acyloxy -OC(O)A wherein A is as defined above;
(6) sulfonyloxy -$OS(O)_2$A wherein A is as defined above;
(7) an acylamino group -NHC(O)A wherein A is as defined above or acylamino -NH-Z wherein Z is a mono, di- or tripeptide composed of D or L α-aminoacids chosen from Ala, Gly, Val, Leu, Ile and Phe and with the terminal amino group either free or acylated by a group -C(O)A or -C(O)OA wherein A is as defined above;

R^2 represents:

(1) A as defined above;
(2) a chlorine or fluorine atom;
(3) a sulphenyl, sulfinyl or sulfonyl group -$S(O)_m$A wherein A is as defined above;
(4) an oxy group -O-A wherein A is as defined above;
(5) an acyl group -C(O)A or acyloxy group -C(O)OA wherein A is as defined above;
(6) on oxymethyl group -CH_2-OA wherein A is as defined above;
(7) a thiomethyl group or a derivative thereof of formula -$CH_2S(O)_m$A wherein m and A are as defined above;
(8) an acyloxymethyl group -$CH_2OC(O)$A or -CH_2O-Z wherein A and Z are as defined above;
(9) an acylthiomethyl group -$CH_2SC(O)$A wherein A is as defined above;
(10) an aminomethyl group -CH_2-N(A)A' wherein A is as defined above and A', being the same or different, is as defined above for A; or A and A' taken together with the nitrogen atom to which they are attached represent a heterocyclic ring;
(11) ammoniomethyl -CH_2N^+(A)(A')A" wherein A and A' are as defined above and A", being the same or different, is as defined for A; or A is alkyl and A' and A" together with the nitrogen atom to which they are attached represent a heterocyclic ring, or A and A' and A" together with the nitrogen atom to which they are attached represent a heterocyclic ring;

(12) an acylaminomethyl group -CH_2NH-C(O)A or -CH_2NH-Z wherein A and Z are as defined above.

2. A compound according to claim 1 having the configuration of formula (I'):



(I')

wherein n is one or two;

A is hydrogen or C_1-C_{12} straight or branched alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_6-C_{10} aryl, C_3-C_8 cycloalkyl, heterocyclyl, 2-phenyl-2-propyl, benzyl or diphenylmethyl, wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl and benzyl groups are either unsubstituted or substituted by fluoro, chloro, sulfo, carboxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, carbamoyl, sulfamoyl, carbamoyloxy, methanesulphonyl, nitro, cyano, diazo, hydroxy, methoxy, ethoxy, tert-butoxy, benzyloxy, benzhydryloxy, acetoxy, pivaloyloxy, benzoxy, carboxymethyl, carboxyphenyl C_6H_5-COOH, carboxybenzyl CH_2-C_6H_5-COOH, benzoyl, pivaloyl, amino, formamido, acetamido, trifluoroacetamido or pivalamido;
B is

(1') a hydrogen atom;
(2') an optionally substituted C_1-C_5 straight or branched alkyl or alkenyl group, or C_3-C_6 cycloalkyl;
(3') optionally substituted C_6-C_{14} aryl;
(4') optionally substituted C_7-C_{14} aralkyl;
(5') optionally substituted heterocyclyl;
(6') optionally substituted (heterocyclyl)alkyl; the substituents for the groups defined under (1')-(6') being selected from fluoro, chloro, bromo, nitro, cyano, sulfo, carboxy, tetrazolyl, C_1-C_4 alkoxycarbonyl, carbamoyl,N-carboxyphenylcarbamoyl, N-carboxybenzylcarbamoyl, N-carboxymethylphenylcarbamoyl, sulfamoyl, carbamoyloxy, methanesulfonyl, hydroxy, C_1-C_4 alkoxy, benzyloxy, benzhydryloxy, phenoxy, p-chlorophenoxy, p-carboxyphenoxy, acetoxy, pivaloyloxy, benzoyloxy, methylthio, phenylthio, methanesulfonyl, benzenesulfonyl, carboxymethylthio, carboxyphenyl C_6H_5-COOH, carboxybenzyl CH_2-C_6H_5-COOH, acetyl, trifluoroacetyl, benzoyl, pivaloyl, amino, dimethylamino, phenylamino, 2,6-dichlorophenylamino diethylamino, formamido, acetamido, trifluoroacetamido, pivalamido, oxo, phenyl, phthalimido, isoindolinyl, 1-oxoisoindolinyl and C_1-C_5 straight or branched alkyl, vinyl or allyl, and C_1-C_4 alkyl substituted by one or more substituents from chloro, fluoro, difluoro, trifluoro, amino, N,N dimethylamino, azido, cyano, carboxy, sulfo, carbamoyl, carbamoyloxy, hydroxy, C_1-C_4 alkyloxycarbonyl, guanidino and a group Y-A"', wherein Y is oxygen, sulphur or carbamoyl(oxy) and A"' is an optionally substituted C_1-C_4 alkyl, phenyl, benzyl or heterocyclic group, the optional substituents being selected from those defined above for groups (1')-(5');

R^1 is

(1') hydrogen or a chlorine, fluorine or bromine atom,
(2') C_1-C_4 alkyl, C_1-C_4 alkenyl, 1-(hydroxy)ethyl, 1-(benzyloxy)ethyl, 1-(benzyloxycarbonyloxy)ethyl, 1-(phenylacetoxy)ethyl, 2-fluoro-1-hydroxyethyl, phenyl or benzyl
(3') methoxy, ethoxy, isopropoxy, phenoxy or benzyloxy
(4') methylthio, ethylthio, isopropylthio
(5') formyloxy, acetoxy or phenylacetoxy
(6') mesyloxy or tosyloxy
(7') formamido, acetamido, fluoroacetamido, trifluoroacetamido or chloroacetamido
(8') R^{iv}-Ala-NH, wherein R^{iv} is acetyl, tert-butoxycarbonyl, benzoxycarbonyl or HOOC-$CH_2CH_2C(O)$-;
(9') R^{iv}-Val-NH, wherein R^{iv} is as defined above;
(10') Val-Pro-NH, LysNH or Ala-Ala-ProNH, wherein the terminal amino group of Val, Lys or Ala respec-

tively or the α-amino group of Lys is either free or acylated with a group R^{iv} as defined above;

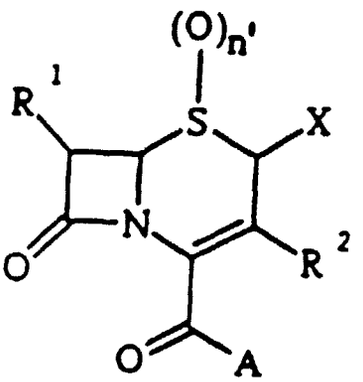
R^2 is either hydrogen or

(1') methyl, chloromethyl, bromomethyl, benzyl, ethyl, propyl or phenyl
(2') chloro
(3') methoxy or benzyloxy
(4') methylthio
(5') formyl, acetyl, benzoyl, carboxy, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl or benzyloxycarbonyl;
(6') methoxymethyl, ethoxymethyl, isopropoxymethyl; or benzyloxymethyl, phenoxymethyl, 3-pyridyloxymethyl wherein the phenyl and pyridyl rings are either unsubstituted or substituted by one group or two groups which are the same or different and are each chosen from hydroxy, carboxy, amino and C_1-C_4 alkoxycarbonyl;
(7') $-CH_2(S)_nA$ wherein n is zero, one or two and A is as defined above or as defined in claim 1;
(8') acetoxymethyl, benzoyloxymethyl, phenylacetoxymethyl or C_3-C_6 alkanoyloxymethyl, which groups are either unsubstituted or substituted by one or more groups selected from carboxy, hydroxy and C_1-C_3 alkoxy;
(9') trialkylammoniomethyl wherein the alkyl group is methyl, ethyl or propyl; N-methylpyrrolidiniomethyl, N-methylpiperidimiomethyl or N-methylmorpholiniomethyl;
(10') pyridiniomethyl which is either unsubstituted or substituted on the heterocyclic ring by fluoro, chloro, methoxy, hydroxy, carboxy or carbamoyl;
(11') carbamoyloxymethyl; or
(12') carboxy;

or a pharmaceutically or veterinarily acceptable salt thereof, or a stereoisomer, epimer, diastereoisomer, geometrical isomer, or tautomer thereof.

3. A process for preparing a compound of the formula (I) as defined in claim 1 or a pharmaceutically or veterinarily acceptable salt thereof, which process comprises:

(i) reacting a compound of formula (II)



(II)

wherein either
(i_a) n' is 0, 1 or 2; A, R^1 and R^2 are as defined in claim 1, and X is a leaving group, with a compound of formula (III)

B-C(O)O-M (III)

wherein B is as defined in claim 1 and M is hydrogen or a metal; or
(i_b) n', A, R^1 and R^2 are as defined above, and X is hydrogen, with a compound of formula (IV)

B-C(O)O-O-W-B' (IV)

wherein B is as defined above and B', being the same or different is as defined above for B, and W is either a bond or a group selected from -C(O)-, -C(O)O-, -$S(O)_2$- and -C(O)NR^v- wherein R^v is phenyl or a C_1-C_4 alkyl group;
(ii) if needed, when n in the compound of formula (I) is of higher value than n' in formula (II) as above defined, oxidizing the obtained compound to a compound of formula (I); and
(iii) if desired, converting the resulting compound of formula (I) into a pharmaceutically or veterinarily acceptable salt thereof and/or, if desired, converting the compound or salt thereof into a stereoisomer, epimer, diastereoisomer, geometrical isomer or tautomer thereof.

4. A process according to claim 3 in which X is bromine, chlorine or iodine, M is hydrogen and the reaction (i_a) is performed in the presence of an inorganic or organic base, optionally in the presence of sodium iodide or potassium iodide, molecular sieves, alumina or calcium oxide, or of silver nitrate, silver perchlorate, silver triflate, copper nitrate or mercury nitrate.

5. A process according to claim 3 or 4 in which the reaction (i_a) is performed in the presence of an organic base selected from triethylamine, diisopropylethylamine, aniline, pyridine, lutidine, collidine, quinoline, N-methylmorpholine, N-methylpyrrolidine and diazabicyclooctane (DABCO); or an inorganic base selected from sodium bicarbonate, calcium carbonate, cesium carbonate and potassium carbonate.

6. A process according to claim 3, 4 or 5 in which X is bromine, chlorine or iodine and M is silver, copper, mercury or lead.

7. A process according to any of claims 3 to 6 in which the reaction (i_a) is carried out in acetonitrile, N,N-dimethylformamide, dichloromethane, tetrahydrofuran, dioxane, ethyl acetate, chloroform, benzene, carbon tetrachloride, diethyl ether, dimethoxyethane, sulpholane, dimethylsulphoxide, hexamethylphosphoramide, N-methyl pyrrolidone, acetone, water or a mixture of any of these at a temperature of from -50°C to +120°C.

8. A process according to claim 3 in which the reaction (i_b) is performed in the presence of 1,5-diazabicyclo[4,3,0] non-5-ene, 1,8-diazabicyclo [5,4,0]undec-7-ene, 1,1,3,3-tetra methylguanidine, 1,4-diazabicyclo[2,2,2] octane, N, N-diiso propylethylamine, N-methylmorpholine, N-methylpyrrolidine, triethylamine, pyridine, lutidine, collidine or quinoline, in acetonitrile, N,N-dimethylformamide, tetrahydrofuran, dioxane, benzene, sulpholane, N,N-dimethylacetamide, hexamethyl phosphoramide, N-methyl pyrrolidone, or a mixture of any of these, at a temperature of -60°C to +40°C.

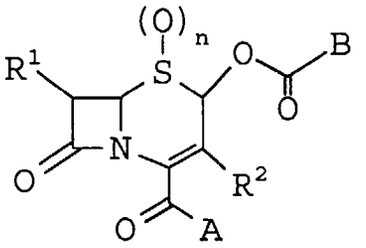
9. A compound of formula (I) or a pharmaceutically or veterinarily acceptable salt thereof, as claimed in claim 1 or 2, for use in a method of treatment of the human or animal body by therapy.

10. A compound or salt according to claim 9 for use as an elastase inhibitor.

11. A pharmaceutical or veterinary composition comprising a suitable carrier and/or diluent and, as an active principle, a compound as claimed in claim 1 or 2 or a pharmaceutically or veterinarily acceptable salt thereof.

Patentansprüche

1. Eine Verbindung mit der Formel (I) oder ein pharmazeutisch oder tierarzneikundlich annehmbares Salz davon;



(I)

worin n Eins oder Zwei ist;

A und B beide unabhängig voneinander entweder Wasserstoff oder ein organisches Radikal ist, das eine beliebig substituierte geradkettige oder verzweigte C_1-C_{12} Alkyl-, C_2-C_{12} Alkenyl-, C_2-C_{12} Alkynyl-, C_6-C_{14} Aryl-, C_3-C_8 Cycloalkyl-, C_5-C_8 Cycloalkenyl- oder C_7-C_{18} Aralkyl-, C_8-C_{18} Aralkenyl-, C_8-C_{18} Aralkynyl-, (Cycloaklyl) alkyl-, (Cycloalkyl)alkenyl-, Heterocyclyl-, (Heterocyclyl)alkyl- und (Heterocyclyl)alkenylgruppe sein kann;
eventuelle Substituenten sind gewählt aus:

- Halo
- Hydroxy;
- Nitro;
- Azido;
- Mercapto
- Amino (z.B. $-NH_2$ oder $-NHR^i$ oder $-NR^iR^{ii}$) wobei R^i und R^{ii}, die entweder beide gleich oder verschieden sein können, geradkettige oder verzweigte C_1-C_{12} Alkyl- oder Phenyl- oder Benzylgruppen sind; oder Phenylcarboxygruppen;
- Formyl
- Cyano;
- Carboxy(alkyl) (z.B. $(CH_2)_tCOOH$ oder $(CH_2)_tCOOR^i$) wobei R^i wie oben definiert ist und t 0, 1, 2 oder 3 ist;
- Sulfo
- Acyl (z.B.-$C(O)R^i$) wobei R^i wie oben definiert oder Trifluoracetyl ist
- Carbamoyl; N-Methylcarbamoyl oder N-Carboxymethylcarbamoyl
- Carbamoyloxy
- Acyloxy (z.B. $-OC(O)R^i$) wobei R^i wie oben definiert oder Formyloxy ist
- Alkoxycarbonyl oder Benzyloxycarbonyl (z.B. $-C(O)OR^i$) wobei Ri wie oben definiert ist;
- Alkoxycarbonyloxy oder Benzyloxycarbonyloxy (z.B. - $OC(O)OR^i$) wobei R^i wie oben definiert ist;
- Alkoxy, Phenoxy oder Benzyloxy (z.B. $-OR^i$) wobei R^i wie oben definiert ist;
- Alkylthio, Phenylthio oder Benzylthio (z.B. $-SR^i$), wobei R^i wie oben definiert ist;
- Alkylsulfinyl, Phenylsulfinyl oder Benzylsulfinyl (z.B. $-S(O)R^i$) wobei R^i wie oben definiert ist;
- Alkylsulfonyl, Phenylsulfonyl oder Benzylsulfonyl (z.B. $-S(O)_2R^i$) wobei R^i wie oben definiert ist;
- Acylamino (z.B. $-NHC(O)R^{iii}$ oder $-NHC(O)R^{iii}$) wobei R^{iii} ein geradkettiges oder verzweigtes C_1-C_{12} Alkyl, Phenyl, Benzyl, CH_2CH_2COOH oder $CH_2CH_2CH_2COOH$ ist;
- Sulfonamido (z.B. $-NHSO_2R^i$) wobei R^i wie oben definiert ist;
- Guanidino (z.B. $NHC(=NH)NH_2$);
- C_1-C_4 Alkyl, C_2-C_4 Alkenyl oder Alkynyl;
- C_3-C_6 Cycloalkyl;
- substituiertes Methyl gewählt aus Chlormethyl, Fluormethyl, Difluormethyl, Trifluormethyl, Aminomethyl, N,N-Dimethylaminomethyl, Azidomethyl, Cyanomethyl, Carboxymethyl, Sulfomethyl, Carbamoylmethyl, Carbomoyloxymethyl, Hydroxymethyl, C_1-C_4 Alkyloxycarbonylmethyl, Guanidinmethyl.
- Phthalimid, Indolyl, Indolinyl, Isoindolinyl, 1-Oxoisoindolinyl;

R1 stellt dar

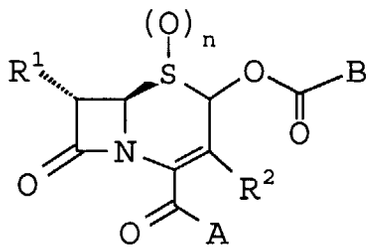
(1) ein Chlor-, Fluor-, Brom- oder Jodatom
(2) A wie oben definiert
(3) ein Äther OA, wobei A wie oben definiert ist

(4) ein Thioäther, Sulfoxid oder Sulfon -S(O)$_m$A, wobei m entweder Null, Eins oder Zwei und A wie oben definiert ist;
(5) Acyloxy -OC(O)A, wobei A wie oben definiert ist;
(6) Sulfonyloxy -OS(O)$_2$A, wobei A wie oben definiert ist;
(7) eine Acylaminogruppe -NHC(O)A, wobei A wie oben definiert ist, oder Acylamino -NH-Z, wobei Z ein Mono- , Di- oder Tripeptid ist bestehend aus D- oder L-α-Aminosäuren, gewählt aus Ala, Gly, Val, Leu, Ile und Phe und mit einer entweder ungebundenen oder durch eine -C(O)A oder -C(O)OA-Gruppe acylierten Aminoendgruppe, wobei A wie oben definiert ist;

R^2 stellt dar:

(1) A wie oben definiert;
(2) ein Chlor- oder Fluoratom;
(3) eine Sulphenyl-, Sulfinyl- oder Sufonylgruppe -S(O)$_m$A, wobei A wie oben definiert ist;
(4) eine Oxygruppe -C-A, wobei A wie oben definiert ist;
(5) eine Acylgruppe -C(O)A oder Acyloxygruppe -C(O)OA, wobei A wie oben definiert ist;
(6) eine Oxymethylgruppe-CH_2-OA, wobei A wie oben definiert ist;
(7) eine Thiomethylgruppe oder ein Derivat davon mit der Formel -CH_2S(O)$_m$A, wobei m und A wie oben definiert sind;
(8) eine Acyloxymethylgruppe-CH_2OC(O)A oder -CH_2O-Z, wobei A und Z wie oben definiert sind;
(9) eine Acylthiomethylgruppe-CH_2SC(O)A, wobei A wie oben definiert ist;
(10) eine Aminomethylgruppe -CH_2-N-(A)A', wobei A wie oben definiert ist und A' entweder gleich oder verschieden sein kann und wie oben für A definiert ist; oder A und A' zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterozyclischen Ring bilden;
(11) Ammoniummethyl -CH_2N^+(A)(A')A", wobei A und A' wie oben definiert sind und A" entweder gleich oder verschieden und wie oben für A definiert ist; oder A Alkyl ist und A' und A" zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterocyclischen Ring bilden, oder A und A' und A" zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen heterocyclischen Ring bilden;
(12) eine Acylaminomethylgruppe -CH_2NH-C(O)A oder -CH_2NH-Z, wobei A und Z wie oben definiert sind.

2. Eine Verbindung gemäß Patentanspruch 1 mit der Konfiguration der Formel (I'):



(I')

worin n Eins oder Zwei ist;

A Wasserstoff oder ein geradkettiges oder verzweigtes C_1-C_{12} Alkyl, C_2-C_{12} Alkenyl, C_2-C_{12} Alkynyl, C_6-C_{10} Aryl, C_3-C_8 Cycloalkyl, Heterocyclyl, 2-Phenyl-2-propyl, Benzyl oder Diphenylmethyl, worin die Alkyl-, Alkenyl-, Alkynyl-, Aryl, Cycloalkyl-, Heterocyclyl- und Benzylgruppen entweder nicht substituiert sind oder substituiert sind durch Fluoro, Chloro, Sulfo, Carboxy, C_1-C_6 Alkoxy, C_1-C_4 Alkoxycarbonyl, Carbamoyl, Sulfamoyl, Carbamoyloxy, Methansulfonyl, Nitro, Cyano, Diazo, Hydroxy, Methoxy, Äthoxy, tert. Butoxy, Benzyloxy, Benzhydryloxy, Acetoxy, Pivaloyloxy, Benzoxy, Carboxymethyl, Carboxyphenyl C_6H_5-COOH, Carboxybenzyl CH_2-C_6H_5-COOH, Benzoyl, Pivaloyl, Amino, Formamido, Acetamido, Trifluoracetamido oder Pivalamido;
B ist

(1') ein Wasserstoffatom
(2') eine beliebig substituierte geradkettige oder verzweigte C_1-C_5 Alkyl- oder Alkenylgruppe, oder C_3-C_6 Cycloalkyl;

(3') ein beliebig substituiertes C_6-C_{14} Aryl;
(4') ein beliebig substituiertes C_7-C_{14} Aralkyl;
(5') ein beliebig substituiertes Heterocyclyl;
(6') ein beliebig substituiertes (Heterocyclyl)alkyl; die Substituenten für die unter (1') - (6') definierten Gruppen sind gewählt aus Fluoro, Chloro, Bromo, Nitro, Cyano, Sulfo, Carboxy, Tetrazolyl, C_1-C_4 Alkoxycarbonyl, Carbamoyl, N-Carboxyphenylcarbamoyl, N-Carboxybenzylcarbamoyl, N-Carboxymethylphenylcarbamoyl, Sulfamoyl, Carbamoyloxy, Methansulfonyl, Hydroxy, C_1-C_4 Alkoxy, Benzyloxy, Benzhydryloxy, Phenoxy, p-Chlorophenoxy, p-Carboxyphenoxy, Acetoxy, Pivaloyloxy, Benzoyloxy, Methylthio, Phenylthio, Methansulfonyl, Benzolsulfonyl, Carboxymethylthio, Carboxyphenyl C_6H_5-COOH, Carboxybenzyl CH_2-C_6H_5-COOH, Acetyl, Trifluoracetyl, Benzoyl, Pivaloyl, Amino, Dimethylamino, Phenylamino, 2,6-Dichlorphenylamino, Diäthylamino, Formamido, Acetamido, Trifluoracetamido, Pivalamido, Oxo, Phenyl, Phthalimido, Isoindolinyl, 1-Oxoisoindolinyl und geradkettiges oder verzweigtes C_1-C_5 Alkyl, Vinyl oder Allyl, und C_1-C_4 Alkyl, das substituiert ist durch einen oder mehrere Substituenten aus Chloro, Fluoro, Difluoro, Trifluoro, Amino, N,N-Dimethylamino, Azido, Cyano, Carboxy, Sulfo, Carbamoyl, Carbamoyloxy, Hydroxy, C_1-C_4 Alkyloxycarbonyl, Guanidino und eine Y-A'''-Gruppe, worin Y Sauerstoff, Schwefel oder Carbamoyl(oxy) und A''' ein beliebig substituiertes C_1-C_4 Alkyl, Phenyl, Benzyl oder eine heterocyclische Gruppe ist, und die Substituenten aus den für oben genannten Gruppen (1') - (5') gewählt sein können;

R^1 ist

(1') Wasserstoff oder ein Chlor-, Fluor- oder Bromatom;
(2') C_1-C_4 Alkyl, C_1-C_4 Alkenyl, 1-(Hydroxy)äthyl, 1-(Benzyloxy)äthyl, 1-(Benzyloxycarbonyloxy)äthyl, 1-(Phenylacetoxy)äthyl, 2-Fluoro-1-hydroxyäthyl, Phenyl oder Benzyl
(3') Methoxy, Äthoxy, Isoprpoxy, Phenoxy oder Benzyloxy
(4') Methylthio, Äthylthio, Isopropylthio
(5') Formyloxy, Acetoxy oder Phenylacetoxy
(6') Mesyloxy oder Tosyloxy
(7') Formamido, Acetamido, Fluoracetamido, Trifluoracetamido oder Chloracetamido (8') R^{iv}-Ala-NH, worin R^{iv} Acetyl, tert. Butoxycarbonyl, Benzoxycarbonyl oder HOOC-$CH_2CH_2C(O)$- ist;
(9') R^{iv}-Val-NH, worin R^{iv} wie oben definiert ist;
(10') Val-Pro-NH, Lys-NH oder Ala-Ala-Pro-NH, worin die Amino-Endgruppe entweder Val, Lys oder Ala oder die α-Aminogruppe von Lys entweder ungebunden oder mit einer R^{iv}-Gruppe wie oben definiert acyliert ist;

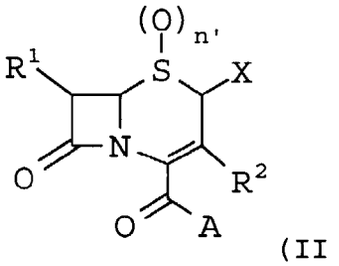
R^2 entweder Wasserstoff ist oder

(1') Methyl, Chlormethyl, Brommethyl, Benzyl, Äthyl, Propyl oder Phenyl
(2') Chloro
(3') Methoxy oder Benzyloxy
(4') Methylthio
(5') Formyl, Acetyl, Benzoyl, Carboxy, Methoxycarbonyl, Äthoxycarbonyl, tert. Butoxycarbonyl oder Benzyloxycarbonyl;
(6') Methoxymethyl, Äthoxymethyl, Isopropoxymethyl; oder Benzyloxymethyl, Phenoxymethyl, 3-Pyridyloxymethyl, wobei die Phenyl- und Pyridil-Ringe entweder nicht substituiert oder substituiert sind durch eine oder zwei Gruppen, die gleich oder verschieden sein können und beide gewählt sind aus Hydroxy, Carboxy, Amino und C_1-C_4 Alkoxycarbonyl;
(7') -$CH_2(S)_nA$, wobei n Null, Eins oder Zwei ist und A wie oben oder wie unter Patentanspruch 1 definiert ist;
(8') Acetoxymethyl, Benzoyloxymethyl, Phenylacetoxymethyl oder C_3-C_6 Alkanolyloxymethyl, deren Gruppen entweder nicht substituiert oder substituiert sind durch eine oder mehrere Gruppen gewählt aus Carboxy, Hydroxy und C_1-C_3 Alkoxy;
(9') Trialkylammoniummethyl, wobei die Alkylgruppe Methyl, Äthyl oder Propyl ist; N-Methylpyrrolidiniummethyl, N-Methylpiperidiniummethyl oder N-Methylmorpholiniummethyl;
(10') Pyridiniummethyl, das entweder nicht substituiert oder substituiert ist am heterocyclischen Ring durch Fluoro, Chloro, Methoxy, Hydroxy, Carboxy oder Carbamoyl;
(11') Carbamoyloxymethyl; oder
(12') Carboxy;

oder ein pharmazeutisch oder tierarzneikundlich annehmbares Salz davon oder ein Stereo-Isomer, Epimer, Diastereo-Isomer, geometrisches Isomer oder ein Tautomer davon.

3. Ein Verfahren zur Herstellung einer Verbindung mit der Formel (I) wie unter Patentanspruch 1 definiert oder eines pharmazeutisch oder tierarzneikundlich annehmbares Salzes davon, bestehend aus:

(i) der Reaktion einer Verbindung mit der Formel (II)



(II

worin entweder
(i_a) n' 0, 1 oder 2 ist; A, R^1 und R^2 wie unter Patentanspruch 1 definiert sind und C eine Restgruppe ist, mit einer Verbindung der Formel (III)

(III) B-C(O)O-M

worin B wie unter Patentanspruch 1 definiert ist und M Wasserstoff oder ein Metall ist; oder
(i_b) n', A, R^1 und R^2 wie oben definiert sind und X Wasserstoff ist, mit einer Verbindung der Formel (IV)

(IV) B-C(O)O-O-W-B'

worin B wie oben definiert ist und B' entweder gleich oder verschieden sein kann und wie oben für B definiert ist und W entweder eine Verbindung oder eine Gruppe ist gewählt aus -C(O)-, -C(O)O-, -$S(O)_2$- und -C(O)NR^v-, worin R^v Phenyl oder eine C_1-C_4 Alkylgruppe ist;
(ii) bei Bedarf, wenn n in der Verbindung der Formel (I) ein höherer Wert ist als n' in der Formel (II) wie oben definiert, Oxidation der erhaltenen Verbindung in eine Verbindung der Formel (I); und
(iii) nach Wunsch, Umwandlung der sich ergebenden Verbindung der Formel (I) in ein pharmazeutisch oder tierarzneikundlich annehmbares Salz davon und/oder nach Wunsch Umwandlung der Verbindung oder ihres Salzes in ein Stereo-Isomer, Epimer, Diastereo-Isomer, geometrisches Isomer oder Tautomer davon.

4. Ein Verfahren gemäß Patentanspruch 3, bei dem X Brom, Chlor oder Jod ist, M Wasserstoff ist und die Reaktion (i_a) in Gegenwart einer anorganischen oder organischen Base durchgeführt wird, nach Wahl in Gegenwart von Natriumjodid oder Kaliumjodid, Molekularsieben, Tonerde oder Calciumoxid, oder von Silbernitrat, Silberperchlorat, Silbertriflat, Kupfernitrat oder Quecksilbernitrat.

5. Ein Verfahren gemäß Patentanspruch 3 oder 4, in dem die Reaktion (i_a) durchgeführt wird in Gegenwart einer organischen Base gewählt aus Triäthylamin, Diisopropyläthylamin, Anilin, Pyridin, Lutidin, Collidin, Chinolin, N-Methylmorpholin, N-Methylpyrrolidin und Diazabicyclooctan (DABCO); oder einer anorganischen Base gewählt aus doppelkohlensaurem Natrium, Calciumcarbonat, Cäsiumcarbonat und Kaliumcarbonat.

6. Ein Verfahren gemäß Patentanspruch 3, 4 oder 5, in dem X Brom, Chlor oder Jod ist und M Silber, Kupfer, Quecksilber oder Blei ist.

7. Ein Verfahren gemäß einem beliebigen der Patentansprüche 3 bis 6, in dem die Reaktion (i_a) in Acetonitril, N,N-Dimethylformamid, Dichlormethan, Tetrahydrofuran, Dioxan, Äthylacetat, Chloroform, Benzol, Kohlenstofftetrachlorid, Diäthyläther, Dimethoxyäthan, Sulfolan, Dimethylsulfoxid, Hexamethylphosphoramid, N-Methylpyrrolidon, Aceton, Wasser oder einem davon beliebig zusammengestellten Gemisch bei einer Temperatur von -50°C bis

+120°C druchgeführt wird.

8. Ein Verfahren gemäß Patentanspruch 3, in dem die Reaktion (i_b) durchgeführt wird in Gegenwart von 1,5-Diazabicyclo[4,3,0]non-5-en, 1,8-Diaza-bicyclo[5,4,0]undec-7-en, 1,1,3,3-Tetramethylguanidin, 1,4-Diaza-bicyclo[2,2,2]octan, N,N-Diisopropyläthylamin, N-Methylmorpholin, N-Methylpryrrolidin, Triäthylamin, Pyridin, Lutidin, Collidin oder Chinolin, in Acetonitril, N,N-Dimethylformamid, Tetrahydrofuran, Dioxan, Benzol, Sulfolan, N,N-Dimethylacetamid, Hexamethyl-phosphoramid, N-Methyl-pyrrolidon oder einem beliebigen Gemisch davon bei einer Temperatur von -60°C bis +40°C.

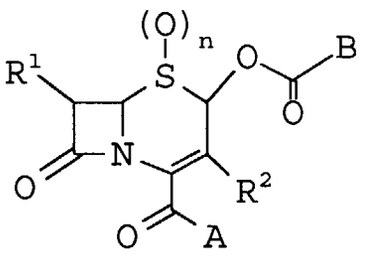
9. Eine Verbindung der Formel (I) oder ein pharmazeutisch oder tierarzneikundlich annehmbares Salz davon wie unter Patentanspruch 1 oder 2 definiert zur Anwendung in einer Behandlungsmethode zur Therapie des menschlichen oder tierischen Körpers.

10. Eine Verbindung oder ein Salz gemäß Patentanspruch 9 zur Anwendung als Elastasehemmer.

11. Eine pharmazeutische oder tierarzneikundliche Zusammensetzung, die einen geeigneten Trägerstoff und/oder ein geeignetes Lösungsmittel und als Wirkstoff eine Verbindung wie in Patentanspruch 1 oder 2 definiert oder ein pharmazeutisch oder tierarzneikundlich annehmbares Sals davon enthält.

Revendications

1. Composé ayant pour formule (I), ou un sel dérivé acceptable du point de vue pharmaceutique ou vétérinaire;



(I)

où n vaut un ou deux:

A et B sont, indifféremment, un hydrogène ou un radical organique choisi parmi les groupes C_1-C_{12} alkyle linéaire ou ramifié, C_2-C_{12} alkényle, C_2-C_{12} alkynyle, C_6-C_{14} aryle, C_3-C_8 cycloalkyle, C_5-C_8 cycloalkényle, C_7-C_{18} aralkyle, C_8-C_{18} aralkényle, C_8-C_{18} aralkynyle, (cycloalkyl)alkyle, (cycloalkyl)alkényle, hétérocyclyle, (hétérocyclyl) alkyle et (hétérocyclyl)alkényle, les dits groupes étant ou non substitués;
dans le cas d'une substitution, les substituants sont choisis parmi les groupes suivants:

- halo;
- hydroxy;
- nitro;
- azido;
- mercapto;
- amino (i.e., $-NH_2$, ou $-NHR^i$ ou $-NR^iR^{ii}$) où R^i et R^{ii}, pouvant être identiques ou différents entre eux, sont des groupes C_1-C_{12} linéaires ou ramifiés alkyle, phényle ou benzyle ; ou phényl carboxy;
- formyle;
- cyano;
- carboxy(alkyle) (i.e., $(CH_2)_tCOOH$ ou $(CH_2)_tCOOR^i$) où R^i est tel que défini ci-dessus et où t vaut 0, 1, 2 ou 3;
- sulfo;
- acyle (i.e., $-C(O)R^i$ où R^i est tel que défini ci-dessus ou trifluoroacétyle;

- carbamoyle, N-méthylcarbamoyle ou N-carboxyméthylcarbamoyle;
- carbamoyloxy;
- acyloxy (i.e., -OC(O)R^i où R^i est tel que défini ci-dessus ou formyloxy;
- alkoxycarbonyle ou benzyloxycarbonyle (i.e., -C(O)OR^i) où R^i est tel que défini ci-dessus;
- alkoxycarbonyloxy ou benzyloxycarbonyloxy (i.e.,-OC(O)OR^i) où R^i est tel que défini ci-dessus;
- alkoxy, phénoxy ou benzyloxy (i.e., -OR^i) où R^i est tel que défini ci-dessus;
- alkylthio, phénylthio ou benzylthio (i.e., -SR^i) où R^i est tel que défini ci-dessus;
- alkylsulfinyle, phénylsulfinyle ou benzylsulfinyle (i.e., -S(O)R^i) où R^i est tel que défini ci-dessus;
- alkylsulfonyle, phénylsulfonyle ou benzylsulfonyle (i.e., -S(O)$_2R^i$) où R^i est tel que défini ci-dessus;
- acylamino (i.e., -NHC(O)R^{iii} ou -NHC(O)OR^{iii}) où R^{iii} est un groupe C_1-C_{12} linéaire ou ramifié alkyle, phényle ou benzyle CH_2CH_2COOH ou $CH_2CH_2CH_2COOH$;
- sulfonamido (i.e., -NHSO_2R^i) où R^i est tel que défini ci-dessus;
- guanidino (i.e., -NHC(=NH)NH_2);
- C_1-C_4 alkyle, C_2-C_4 alkényle ou alkynyle;
- C_3-C_6 cycloalkyle;
- méthyle substitué choisi parmi chlorométhyle, fluorométhyle, difluorométhyle, trifluorométhyle, aminométhyle, N,N-diméthylaminométhyle, azidométhyle, cyanométhyle, carboxyméthyle, sulfométhyle, carbamoylméthyle, carbamoyloxyméthyle, hydroxyméthyle, C_1-C_4 alkyloxycarbonylméthyle, guanidinométhyle.
- phtalimido, indolyle, indolinyle, isoindolinyle, 1-oxoisoindolinyle;

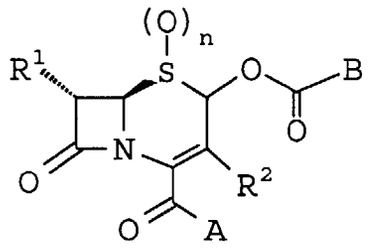
R1 represente

(1) un atome de chlorine, fluorine, bromine ou iodine;
(2) A tel que défini ci-dessus;
(3) un éther OA où A est tel que défini ci-dessus;
(4) un thioéther, sulfoxide ou sulfone -S(O)$_m$ A où m vaut zéro, un ou deux et A est tel que défini ci-dessus;
(5) acyloxy -OC(O)A où A est tel que défini ci-dessus;
(6) sulfonyloxy -OS(O)$_2$A où A est tel que défini ci-dessus;
(7) un groupe acylamino -NHC(O)A où A est tel que défini ci-dessus ou acylamino -NH-Z où Z est un mono-, di- ou tripeptide constitué par des D- et L-acides aminés α choisis parmi Ala, Gly, Val, Leu, Ile et Phe dont le groupe amino-terminal est libre ou acylé par un groupe -C(O)A ou -C(O)OA où A est tel que défini ci-dessus;

R^2 représente:

(1) A tel que défini ci-dessus;
(2) un atome de chlorine ou fluorine;
(3) un groupe sulphényle, sulfinyle ou sulfonyle -S(O)$_m$A où A est tel que défini ci-dessus;
(4) un groupe oxy -O-A où A est tel que défini ci-dessus;
(5) un groupe acyle -C(O)A ou un groupe acyloxy -C(O)OA où A est tel que défini ci-dessus;
(6) un groupe oxyméthyle -CH_2-OA où A est tel que défini ci-dessus;
(7) un groupe thiométhyle ou un de ses dérivés de formule-CH_2S(O)$_m$A où m et A sont tels que définis ci-dessus;
(8) un groupe acyloxyméthyle -CH_2OC(O)A ou -CH_2O-Z où A et Z sont tels que définis ci-dessus;
(9) un groupe acylthiométhyle -CH_2SC(O)A où A est tel que défini ci-dessus;
(10) un groupe aminométhyle -CH_2-N(A)A' où A est tel que défini ci-dessus et A', étant identique ou différent, est tel que defini ci-dessus pour A; ou A et A' pris ensemble avec l'atome d'azote auquel ils sont liés représentent un noyau hétérocyclique;
(11) un groupe ammoniométhyle -CH_2N^+(A)(A')A" où A et A' sont tels que définis ci-dessus et A", étant identique ou différent, est tel que defini ci-dessus pour A; ou A est alkyle et A' et A" pris ensemble avec l'atome d'azote auquel ils sont liés représentent un noyau hétérocyclique; ou A, A' et A" pris ensemble avec l'atome d'azote auquel ils sont liés représentent un noyau hétérocyclique;
(12) un groupe acylaminométhyle -CH_2NH-C(O)A ou -CH_2NH-Z où A et Z sont tels que définis ci-dessus.

2. Composé selon la revendication 1 ayant la configuration donnée par la formule (I'):



(I')

où n vaut un ou deux;

A est hydrogène ou C_1-C_{12} alkyle linéaire ou ramifié, C_2-C_{12} alkényle, C_2-C_{12} alkynyle, C_6-C_{10} aryle, C_3-C_8 cycloalkyle, hétérocyclyle, 2-phényl-2-propyle, benzyle ou diphénylméthyle, les dits groupes alkyle, alkényle, alkynyle, aryle, cycloalkyle, hétérocyclyle et benzyle étant ou non substitués par fluoro, chloro, sulfo, carboxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyle, carbamoyle, sulfamoyle, carbamoyloxy, méthanesulfonyle, nitro, cyano, diazo, hydroxy, méthoxy, éthoxy, tert-butoxy, benzyloxy, benzhydryloxy, acétoxy, pivaloyloxy, benzoxy, carboxyméthyle, carboxyphényle C_6H_5-COOH, carboxybenzyle CH_2-C_6H_5-COOH, benzoyle, pivaloyle, amino, formamido, acétamido, trifluoroacétamido ou pivalamido;
B est

(1') un atome d'hydrogène;
(2') un groupe C_1-C_5 linéaire ou ramifié alkyle ou alkényle éventuellement substitué, ou C_3-C_6 cycloalkyle;
(3') C_6-C_{14} aryle éventuellement substitué;
(4') C_7-C_{14} aralkyle éventuellement substitué;
(5') hétérocyclyle éventuellement substitué;
(6') (hétérocyclyl)alkyle éventuellement substitué; les substituants pour les groupes définis dans (1') à (6') étant choisis parmi fluoro, chloro, bromo, nitro, cyano, sulfo, carboxy, tétrazolyle, C_1-C_4 alkoxycarbonyle, carbamoyle, N-carboxyphénylcarbamoyle, N-carboxybenzylcarbamoyle, N-carboxyméthylphénylcarbamoyle, sulfamoyle, carbamoyloxy, méthanesulfonyle, hydroxy, C_1-C_4 alkoxy, benzyloxy, benzhydryloxy, phénoxy, p-chlorophénoxy, p-carboxyphénoxy, acétoxy, pivaloyloxy, benzoyloxy, méthylthio, phénylthio, méthanesulfonyle, benzènesulfonyle, carboxyméthylthio, carboxyphényle C_6H_5-COOH, carboxybenzyle CH_2-C_6H_5-COOH, acétyle, trifluoroacétyle, benzoyle, pivaloyle, amino, diméthylamino, phénylamino, 2,6-dichlorophénylamino, diéthylamino, formamido, acétamido, trifluoroacétamido, pivalamido, oxo, phényle, phtalimido, isoindolinyle, 1-oxoisoindolinyle et C_1-C_5 alkyle linéaire ou ramifié, vinyle ou allyle, et C_1-C_4 alkyle substitué par un ou plusieurs substituants parmi chloro, fluoro, difluoro, trifluoro, amino, N, N diméthylamino, azido, carboxy, sulfo, carbamoyle, carbamoyloxy, hydroxy, C_1-C_4 alkyloxycarbonyle, guanidino et un groupe Y-A''', où Y est oxygène, soufre ou carbamoyl(oxy) et A''' est un groupe éventuellement substitué C_1-C_4 alkyle, phényle, benzyle, ou hétérocyclique, les substituants éventuels étant choisis parmi ceux définis ci-dessus pour les groupes (1') à (5');

R^1 est

(1') hydrogène ou un atome de chlorine, fluorine ou bromide;
(2') C_1-C_4 alkyle, C_1-C_4 alkényle, 1-(hydroxy)éthyle, 1-(benzyloxy)éthyle, 1-(benzyloxycarbonyloxy)éthyle, 1-(phénylacétoxy)éthyle, 2-fluoro-1-hydroxyéthyle, phényle ou benzyle;
(3') méthoxy, éthoxy, isopropoxy, phénoxy ou benzyloxy;
(4') méthylthio, éthylthio, isopropylthio;
(5') formyloxy, acétoxy ou phénylacétoxy;
(6') mésyloxy ou tosyloxy;
(7') formamido, acétamido, fluoroacétamido, trifluoroacétamido ou chloroacétamido;
(8') R^{iV}-Ala-NH, où R^{iV} est acétyle, tert-butoxycarbonyle, benzoxycarbonyle ou HOOC-$CH_2CH_2C(O)$-;
(9') R^{iv}-Val-NH, où R^{iv} est tel que défini ci-dessus;
(10') Val-Pro-NH, Lys-NH ou Ala-Ala-Pro-NH, où le groupe amino-terminal de Val, Lys ou Ala respectivement ou le groupe α-amino de Lys est libre ou acétylé par un groupe R^{iv} comme défini ci-dessus;

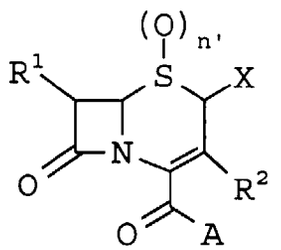
R^2 est soit hydrogène soit

(1') méthyle, chlorométhyle, bromométhyle, benzyle, éthyle, propyle ou phényle;
(2') chloro;
(3') méthoxy ou benzyloxy;
(4') méthylthio;
(5') formyle, acétyle, benzoyle, carboxy, méthoxycarbonyle, éthoxycarbonyle, tert-butoxycarbonyle ou benzyloxycarbonyle;
(6') méthoxyméthyle, éthoxyméthyle, isopropoxyméthyle; ou benzyloxyméthyle, phénoxyméthyle, 3-pyridyloxyméthyle, les dits noyaux phényle et pyridyle étant ou non substitués par un ou deux groupes identiques ou différents choisis parmi hydroxy, carboxy, amino et C_1-C_4 alkoxycarbonyle;
(7') $-CH_2(S)_nA$ où n vaut zéro, un ou deux et A est tel que défini ci-dessus ou tel que défini à la revendication 1;
(8') acétoxyméthyle, benzoyloxyméthyle, phénylacétoxyméthyle ou C_3-C_6 alkanoyloxyméthyle, les dits groupes étant ou non substitués par un ou plusieurs groupes choisi parmi carboxy, hydroxy et C_1-C_3 alkoxy;
(9') trialkylammoniométhyle où le groupe alkyle est méthyle, éthyle ou propyle; N-méthylpyrrolidiniométhyle, N-méthylpiperidiniométhyle ou N-méthylmorpholiniométhyle;
(10') pyridiniométhyle qui est ou non substitué sur le noyau hétérocyclique par un groupe fluoro, chloro, méthoxy, hydroxy, carboxy ou carbamoyle;
(11') carbamoyloxyméthyle; ou
(12') carboxy;

ou un sel dérivé acceptable du point de vue pharmaceutique et vétérinaire, ou un stéréoisomère, épimère, diastéréoisomère, isomère géométrique, ou tautomère dérivé.

3. Procédé pour la préparation d'un composé de formule (I) selon la revendication 1 ou d'un de ses sels dérivés acceptable du point de vue pharmaceutique et vétérinaire, lequel procédé comprend:

(i) la réaction d'un composé de formule (II)



(II)

dans laquelle
(i_a) n' vaut 0, 1 ou 2; A, R^1 et R^2 sont tels que défini à la revendication 1 et X est un groupe partant, avec un composé de formule (III)

(III) B-C (O) O-M

où B est tel que défini à la revendication 1 et M est hydrogène ou un métal; ou bien
(i_b) n', A, R^1 et R^2 sont tels que défini ci-dessus et X est hydrogène, avec un composé de formule (IV)

(IV) B-C(O)O-O-W-B'

où B est tel que défini ci-dessus et B', étant identique ou différent, est tel que défini ci-dessus pour B, et W est une liaison ou un groupe choisi parmi -C(O)-, -C(O)O-, $-S(O)_2$- et $-C(O)NR^v$- où R^v est un groupe phényle ou C_1-C_4 alkyle;

(ii) si cela est nécessaire, lorsque la valeur de n dans le composé de formule (I) est supérieure à celle de n' dans le composé de formule (II) tels que définis ci-dessus, l'oxydation du composé obtenu en un composé de formule (I); et
(iii) si cela est souhaité, la conversion du composé résultant de formule (I) en un de ses sels dérivés acceptable du point de vue pharmaceutique et vétérinaire et/ou, si cela est souhaité, la conversion du composé ou du sel dérivé en un stéréoisomère, épimère, diastéréoisomère, isomère géométrique, ou tautomère dérivé.

4. Procédé selon la revendication 3 dans lequel X est bromine, chlorine ou iodine, M est hydrogène et la réaction (i_a) est conduite en présence d'une base organique ou inorganique, éventuellement en présence de iodure de sodium, iodure de potassium, sieves moléculaires, oxide d'aluminium ou de calcium, ou de nitrate d'argent, perchlorate d'argent, triflate d'argent, nitrate de cuivre ou nitrate de mercure.

5. Procédé selon la revendication 3 ou 4 dans lequel la réaction (i_a) est conduite en présence d'une base organique choisie parmi triéthylamine, diisopropyléthylamine, aniline, pyridine, lutidine, collidine, quinoline, N-méthylmorpholine, N-méthylpyrrolidine et diazabicyclooctane (DABCO); ou d'une base inorganique choisie parmi bicarbonate de sodium, carbonate de calcium, carbonate de césium et carbonate de potassium.

6. Procédé selon la revendication 3, 4 ou 5 dans lequel X est bromine, chlorine ou iodine et M est argent, cuivre, mercure ou lead.

7. Procédé selon l'une des revendications 3 à 6 dans lequel la réaction (i_a) est conduite dans un solvant acétonitrile, N,N-diméthylformamide, dichlorométhane, tétrahydrofurane, dioxane, acétate d'éthyle, chloroforme, benzène, tétrachlorure de carbone, diéthyl éther, diméthoxyéthane, sulfolane, diméthylsulfoxide, hexaméthyl phosphoramide, N-méthyl pyrrolidone, acétone, eau ou tout mélange formé de ces réactifs, à une température comprise entre -50°C et +120°C.

8. Procédé selon la revendication 3 dans lequel la réaction (i_b) est conduite en présence de 1,5-diazabicyclo[4,3,0] non-5-ène, 1,8-diazabicyclo[5,4,0]undec-7-ène, 1,1,3,3-tétra méthylguanidine, 1,4-diazabicyclo[2,2,2] octane, N, N-diiso propyléthylamine, N-méthylmorpholine, N-méthylpyrrolidine, triéthylamine, pyridine, lutidine, collidine ou quinoline, dans un solvant acétonitrile, N,N-diméthylformamide, tétrahydrofurane, dioxane, benzène, sulfolane, N,N-diméthylacétamide, hexaméthyl phosphoramide, N-méthyl pyrrolidone, ou tout mélange formé de ces réactifs, à une température comprise entre -60°C et +40°C.

9. Composé de formule (I) ou un de ses sels dérivés acceptable du point de vue pharmaceutique et vétérinaire, selon la revendication 1 ou 2, pour utilisation dans une méthode thérapeutique appliquée au traitement du corps humain ou animal.

10. Composé ou sel selon la revendication 9 pour utilisation comme inhibiteur de l'élastase.

11. Une composition pharmaceutique ou vétérinaire constituée d'un "carrier" et/ou d'un diluant approprié et, comme principe actif, d'un composé ou sel dérivé acceptable du point de vue pharmaceutique et vétérinaire tel que défini à la revendication 1 ou 2.